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STUDIES WITH DUST EXTRACTS

HOMER E. PRINCE, M.D., F.A.C.A.
Crockett, Texas

T. S. PAINTER, JR., M.D., F.A.C.A., MARIE B. MORROW, Ph.D., F.A.C.A., and GEORGE H. MEYER, M.A.
Austin, Texas

IN 1958, The Association of Allergists for Mycological Investigations began a collaborative study of the allergenicity of dusts from various environments for patients sensitive to house dust. We believed that more information on this point would be worth while, because patients sensitive to house dust often have symptoms when exposed to dust in other environments, and since dusts from sources other than homes are frequently employed for the preparation of diagnostic and therapeutic dust allergens.

An ultimate objective of these studies was confirmation of the observations of others, suggesting the importance of molds in determining allergenic variations in dusts of various sources and geographic areas. Conant, Wagner and Rackemann[1] found high numbers of molds without characteristic flora in dusts from various sources in 1936. The next year, Wagner and Rackemann[5] suspected, but did not prove conclusively, that the

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The following physicians collaborated in these studies: John W. Argabrite, M.D., Watertown, South Dakota; William H. Browning, M.D., Shreveport, Louisiana; Lester L. Bartlett, M.D., Pittsburgh, Pennsylvania; Clifton R. Brooks, M.D., Wheaton, Maryland; K. J. Bierlein, M.D., Pittsburg, Kansas; Ethan Allan Brown, M.D., Boston, Massachusetts; Alan G. Cazort, M.D., Little Rock, Arkansas; Rita L. Don, M.D., El Paso, Texas; R. L. Etter, M.D., W. J. Raymer, M.D., R. H. Jackson, M.D., Houston, Texas; Ben C. Eisenberg, M.D., Huntington Park, California; Meryl M. Fenton, M.D., Detroit, Michigan; Lois Frayser, M.D., Seattle, Washington; James Holman, M.D., Dallas, Texas; L. Dell Henry, M.D., Ann Arbor, Michigan; Lawrence J. Halpin, M.D., Cedar Rapids, Iowa; Dick Huff, M.D., Oklahoma City, Oklahoma; Ralph Hale, M.D., Wichita, Kansas; James A. Mansmann, M.D., Pittsburgh, Pennsylvania; George W. Owen, M.D., Jackson, Mississippi; Edna S. Pennington M.D., Nashville, Tennessee; Sam Sanders, M.D., Memphis, Tennessee; Boen Swinny, M.D., San Antonio, Texas; Herschel E. Whigham, M.D., McAllen, Texas; Orval R. Withers, M.D., Kansas City, Missouri.

TABLE I. SOURCES AND VARIATIONS IN PREPARATION OF DUST EXTRACTS

Code Number	Pooled Vacuum Cleaner House Dust	Special Sources	Dialysate		Acetone Precipitated		Not Precipitated
			Water	Buffered Water	Slow Removal	Rapid Removal	
4B2	Texas, Pennsylvania, California		X		X		
4B20 A	Texas			X			X
4B20 B				X		X	
4B22 A	California			X			X
4B22 B				X		X	
4B26	Pennsylvania			X			X
4B30	Little Rock, Ark., Memphis, Tenn.			X			X
4B100		Dept. store, Boston, Mass.	X		X		
4B201		Hotel, San Antonio, Texas	X		X		
4B202		Hotel, Cedar Rapids, Iowa	X		X		
4B301		Men's and Women's dormitories, Cedar Rapids, Iowa	X		X		
4B302		Men's dormitory, Austin, Texas	X		X		
4B1		Old feather pillows Houston, Texas	X		X		
4B7 A		Houston, Texas		X			X
4B7 B		Houston, Texas		X		X	
4B307		Physician's office, Shreveport, La.		X			X

presence of molds may determine the allergenicity of kapok or cotton. In other reports, Wallace, Weaver and Scherago,[6] in 1950, Swaebly and Christensen,[3] in 1952, as well as Schaffer, Seidman and Bruskin,[2] in 1953, have called attention to the high mold content of dusts from homes, and have pointed out wide variation in the mold flora of different dusts. Van der Werff[4] noted significant variations in the allergenicity of house dusts from certain geographic areas or even from homes in the same community which he attributed to differences in mold flora.

Early in these studies, it became obvious that vacuum cleaner house dust from the homes of patients sensitive to house dust had a much higher allergen content than did dust from any other source under investigation. This anticipated finding justified concentration of our efforts since 1959 on studies with vacuum cleaner house dust only, with particular attention to the influence of geographic origin.

SOURCES OF DUST

(a) *House Dust.*—Pooled vacuum cleaner house dust from the homes of their dust-sensitive patients was submitted to the laboratory by the physicians collaborating in these studies. To insure the greatest allergenicity of all dust specimens, a particular effort was made to secure the dust obtained from the homes of new dust sensitive patients during thorough house cleaning procedures in compliance with routine dust control instructions. In order to minimize geographic influences, house dusts from several widely separated areas were combined in one extract (4B2) intended for use as a representative vacuum cleaner house dust allergen in comparative tests with dusts from other sources. Otherwise, the pooled dusts were either processed individually when they represented distinct geographic regions, or several dusts from less widely separated areas were combined on a representative regional basis.

(b) *Special Dusts.*—Vacuum cleaner dust was collected from hotels, dormitories, a physician's office, and a department store, by coincidence representing widely separated areas. It was thought that the particular sources of origin of these dusts would be the most important determinant of allergenic variation, although geographic factors might also be involved.

(c) *Feather Pillow Dust.*—One of the special dusts selected for study deserves further comment. For several years, extract of feather dust, the by-product of a dry cleaning process employed in the renovation of old feather pillows, has been observed to react frequently in a great many patients sensitive to house dust. These reactions ordinarily have been considered as dust reactions, with no implication of sensitivity to fresh feathers. This frequent parallelism of reactivity between our locally collected house dust and feather pillow dust suggested inclusion of the latter in these studies. Another purpose for including the feather pillow dust was to secure additional preliminary data for further investigations now in progress, and which will be the subject of a future report.

The sources of all the dusts are shown in Table I.

EXTRACTION TECHNIQUE

Since 1948, one of us has used dialyzed, acetone precipitated extracts of pooled vacuum cleaner house dust from patients' homes in the Houston, Texas, area for both diagnosis and treatment. Because this method of extraction produced uniform allergen solutions from house dust, we employed it for all dusts chosen as representative of various sources in the first phase of these investigations. The essential steps of this technique as adapted to dust extraction are shown schematically in Figure 1.

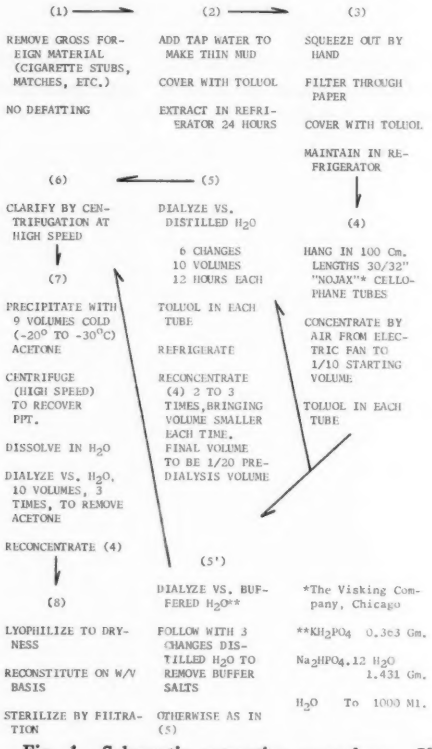

Fig. 1. Schematic extraction procedures. If it is not desired to employ acetone precipitation, step 7 may be omitted.

For some of our later extracts, we varied the extraction procedure by omitting acetone precipitation, and for others we employed buffered water for dialysis. In the preparation of those extracts in which we desired to study the effects of acetone precipitation, we divided the dialyzed and concentrated extract into two portions, one for precipitation with acetone, the other for completion without precipitation. We modified the precipitation step itself in some of our later extractions by removing the acetone

within a period of 90 minutes instead of allowing it to remain for a convenient, unspecified time as we had done earlier (Table I).

All the extracts employed in these studies, by whatever modification of preparation, were reconstituted in glycero-saline in a ratio of 1:50.

CLINICAL STUDIES

For tests by the collaborating physicians, the allergens were arranged in groups in keeping with the comparisons desired. An effort was made to distribute these sets in a manner which would permit the investigators to study extracts of dust collected in their communities; the allergens were in every instance also tested on patients residing in distant areas. A few of the investigators, on the other hand, were supplied all the extracts, although not at the same time. Since the various comparative studies were made at different times, it was impossible for all the allergens to be tested on each patient. However, the comparisons of the extracts in the respective groups were made by tests on the same patients, and at the same time.

The extracts were employed in tests on patients sensitive to house dust to determine their allergenic behavior, and in tests on non-sensitive persons to demonstrate their freedom from irritating properties. Whether or not patients were sensitive to dust was reported by the collaborators, on the basis of prior tests with other dust extracts, or of clinical impressions. But in accepting such classification for the purposes of this study, we imposed the criterion that to be considered sensitive a patient must have reacted to at least one of the extracts in the test series. This qualification assured that our test subjects were sensitive to one or more of the dust extracts at the time their skin tests were performed. The tests were made by the scratch or pressure puncture technique with the 1:50 concentrates; these were followed by intradermal tests with dilutions ranging from 1:5,000 to 1:500,000, or occasionally 1:5,000,000.

In planning the testing routine, we had hoped that the intradermal tests, made with increasing strengths of allergens, would give us information of a quantitative nature concerning the relative allergenicity of the various extracts. Because the starting strength was frequently not below the reacting level, or the tests were not conducted uniformly, the composite data from the intradermal tests afforded very little statistical information, although such tests reported by individual investigators suggested differences in reactivity of some of the extracts. The results of the scratch or pressure puncture tests, on the other hand, showed definite differences. Accordingly, we accepted the number of unequivocal reactions to scratch or pressure puncture tests as an indication of the reactivity of the dust extracts.

RESULTS

The results of the tests with the various dust extracts are shown in Tables II through IV. The tables represent composite findings of several investiga-

tors. Except as specified in Table III B and III C, different tables deal with different groups of patients, but the tests recorded in each table were performed on the same patients.

As shown in Table II A and II B, and Table IV, an extract of house dust reacted more frequently than did extracts of dust from other sources, except dust from one dormitory, and from old feather pillows.

TABLE II. REACTIVITY OF DUSTS FROM VARIOUS SOURCES AS DETERMINED BY SCRATCH TESTS ON PATIENTS SENSITIVE TO HOUSE DUST

Code Number	Source and Area	Number of Patients Tested	Number of Positive Scratch Tests	Per Cent Reacting
	A			
4B2	House dust (Texas, Pennsylvania, California)	62	40	64
4B201	Hotel dust (San Antonio, Texas)	62	28	45
4B202	Hotel dust (Cedar Rapids, Iowa)	62	21	34
4B301	Men's and women's dormitories, (Cedar Rapids, Iowa)	62	25	40
4B302	Men's dormitory (Austin, Texas)	62	40	64
	B			
4B2	House dust (Texas, Pennsylvania, California)	131	89	67
4B100	Department store dust (Boston, Massachusetts)	131	32	27
4B1	Feather pillow dust (Houston, Texas)	131	87	67

All extracts dialyzed against distilled water.
All extracts precipitated with acetone.

Tables III A, III B, and III C disclose that a single precipitation with cold acetone does not enhance the allergenicity of extracts of house dust, or old feather dust, as determined by the number of reactions to scratch tests on patients sensitive to house dust.

Table IV reveals no significant differences in the number of positive skin tests produced in sensitive patients by extracts of pooled house dust from widely separated areas. Furthermore, in a careful study of the test records we could discover no greater frequency of reaction of any of the dust extracts on local patients than on patients residing in distant areas.

In tests on normal persons, or allergic patients not sensitive to house dust, there was no indication of non-specific reactivity of any of the dust extracts under investigation.

HOUSE DUST CONSTITUENTS

Constituents we have encountered in different dusts by microscopic study can be seen in Table V. These are shown for certain of the dusts from various areas in Table VI.

DISCUSSION

Other observations point to the correctness of our conclusions that dusts from other environments are less allergenic than house dust for patients sensitive to house dust. For example, we were not surprised to find the low relative rating from the department store dust, which contained a minimum of lint of the type ordinarily associated with highly allergenic dust. Also,

TABLE III. EFFECTS OF SINGLE PRECIPITATION WITH ACETONE IN PREPARATION OF DUST EXTRACTS, AS DETERMINED BY SCRATCH TESTS ON PATIENTS SENSITIVE TO HOUSE DUST

Code Number	Source and Area	Not Precipitated	Precipitated With Acetone	Number of Patients Tested	Number of Positive Scratch Tests	Per Cent Reacting
		A				
4B20 A	House dust (East and South Texas)	X		67	57	85
4B20 B	House dust (East and South Texas)		X	67	55	82
4B22 A	House dust (San Francisco, California)	X		67	54	81
4B22 B	House dust (San Francisco, California)		X	67	56	84
		B				
4B20 A	House dust (East and South Texas)	X		63*	54	86
4B20 B	House dust (East and South Texas)		X	63	55	87
4B22 A	House dust (San Francisco, California)	X		63	52	83
4B22 B	House dust (San Francisco, California)		X	63	47	75
		C				
4B7 A	Feather pillow dust (Houston, Texas)	X		57*	32	56
4B7 B	Feather pillow dust (Houston, Texas)		X	57	31	54

All extracts dialyzed against buffered water.
Acetone removed rapidly from all precipitated extracts.
*The 63 patients in Table III B include the 57 patients in Table III C.

the increasing use of synthetic furnishings, along with more efficient cleaning procedures, explains the general observation that not as many patients sensitive to house dust experience symptoms in most hotels as they did a few years ago. Dust from the hotel in San Antonio was formerly employed for the routine preparation of extracts, but within the past five years extracts prepared from this dust have not been sufficiently reactive to justify their continued use.

Our earlier pooled extract of house dust (4B2) seemed to be less reactive than did 4B20 and subsequent lots. While the earlier extract was not tested simultaneously with extracts of the other house dusts, nor on the same patients, it and the other lots reacted similarly on tests in two groups of patients. The data suggest decreased allergenicity of those extracts in the preparation of which acetone was allowed to remain in contact with the precipitate for long periods, or increased activity of extracts prepared by

TABLE IV. REACTIVITY OF EXTRACTS OF VACUUM CLEANER HOUSE DUST FROM VARIOUS AREAS AND OF DUST FROM AN OFFICE, AS DETERMINED BY SCRATCH TESTS ON PATIENTS SENSITIVE TO HOUSE DUST

Code Number	Area	Number of Patients Tested	Number of Positive Scratch Tests	Per Cent Reacting
4B20 A	East and South Texas	67	57	85
4B22 A	San Francisco, California	67	54	81
4B26	Pittsburgh, Pennsylvania	67	54	81
4B30	Little Rock, Arkansas, Memphis, Tennessee	67	53	79
4B307	Physician's office, Shreveport, Louisiana	67	40	59

All extracts dialyzed against buffered water.
All extracts prepared without acetone precipitation.

TABLE V. COMPOSITE MICROSCOPIC FINDINGS IN VACUUM CLEANER HOUSE DUST

Molds		Bacteria	Pollen	Miscellaneous	Insects	Plant Material	Synthetic Fibers
Alternaria	Epicoccum	Bacilli	Pine	Mites	Wing scales	Plant tissue	Dyed threads
Helminthosporium	Fusarium	Cocci	Grass	Animal tissue	Body parts	Plant hairs	Other
Curvularia	Dicoccum		Ragweed	Animal hairs		Plant debris	
Hormodendrum	Tetraploa		Other	Feather pinnules			
Pullularia	Cryptococcus			Cotton fibers			
Aspergillus	Rust spores			Cellulose (paper)			
Penicillium	Smut spores			Starch grains			
Trichoderma	Other spores			Carbon			
Scopulariopsis	Mycelial fragments			Silica particles (sand)			
Papularia							

TABLE VI. MICROSCOPIC FINDINGS OF VACUUM CLEANER HOUSE DUST AND DUST FROM OLD FEATHER PILLOWS

	House Dusts				Feather Dust
	Texas	S. Fran., Calif.	Pitts., Penn.	L. Rock-Memphis	Houston, Tex.
	4B20	4B22	4B26	4B30	4B7
Alternaria	x			x	
Helminthosporium	x		x	x	
Curvularia	x		x		
Hormodendrum	x	x	x		
Aspergillus	x	x	x	x	
Fusarium	x				
Undetermined spores	x	x			
Mycelial fragments	x	x			
Bacterial cells			x	x	
Insect scales	x	x			
Insect parts	x	x	x	x	
Plant tissue	x	x	x	x	x
Plant hairs	x	x	x	x	x
Plant debris	x	x	x	x	x
Animal tissue			x	x	
Animal hairs			x	x	
Cellulose fibers	x	x	x	x	
Synthetic fibers	x	x	x	x	
Feather pinnules			x	x	xx
Starch grains			x	x	
Pollen: (a) pine	x				
(b) other		x	x	x	
Inorganic materials, (carbon, silica)	x	x			

dialysis against buffered water. Unfortunately, we did not divide the preliminary extracts of any of the dusts into aliquot portions, for better comparison on these points.

Our results are conclusive regarding the lack of any advantage which might be gained by a single precipitation with acetone. In the case of extracts of vacuum cleaner house dust in which precipitates were produced readily with acetone, the amount of the precipitated material was 83 per cent in one extract (4B22 B), and 55 per cent in another (4B20 B), in comparison with the weight of the lyophilized solids in the non-precipitated counterpart. With the feather dust extract, however, precipitation was only partial, resulting in greatly reduced quantity of precipitate and a turbid, opalescent appearance of the supernatant from which additional precipitate could not be recovered by ordinary centrifugation. In one lot of feather pillow dust (4B7 B), 14 per cent of the total extractable material was precipitated with acetone. Acetone precipitation in the case of the feather pillow dust extract would be advantageous provided it could be assumed that this treatment accomplishes *selective* precipitation of allergenic material, thereby fractionating active allergens from non-reactive portions. On the basis of this assumption in the case of the feather pillow dust, the advantage would be at least seven fold. However, the acetone precipitated extract did not appear clinically to possess such advantage. Neither was there an anticipated clinical advantage of two to one in the acetone precipitated extract (4B20 B) of house dust. After we could find no advantage from acetone precipitation of any of the extracts, and since this step is uneconomical from the standpoint of reduced yields, we discontinued its routine use.

The microscopic findings of house dust from various geographic areas as revealed in Table VI are surprisingly uniform. This lack of variation of any of the constituents, including the mold flora, coincides with our failure to find differences in the allergenicity of house dust on the basis of geographic origin. Our studies, therefore, are not conclusive regarding the part played by molds in determining differences in the allergenicity of house dust. We shall note, however, that high allergenicity of feather dust for patients sensitive to house dust does not seem to be predicated on the mold content.

SUMMARY

1. Extracts of house dust from homes of patients sensitive to dust reacted more frequently in dust-sensitive patients than did extracts of dust from two hotels, a department store, a physician's office, and one dormitory, and with a frequency equal to that of an extract of dust from another dormitory.

2. There was no difference in the reactivity of extracts of house dust prepared with or without a single precipitation with acetone.

3. The geographic area from which vacuum cleaner house dust was obtained made no difference in its allergenicity.

4. No essential differences were noted in the microscopic constituents of vacuum cleaner house dusts from widely separated areas.

SUMMARY FOR TABLES

No differences attributable to geographic origin or microscopic constituents were noted in the allergenicity of house dust. House dust is more allergenic for dust-sensitive patients than is dust from several other sources.

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P.O. Box 901

MOLDS OF ALLERGENIC SIGNIFICANCE IN THE PUGET SOUND AREA

JOHN COLEN, M.D., F.A.C.A., and PAUL P. VAN ARSDEL, JR., M.D.
with the technical assistance of
MRS. SUE STEVENS and MRS. FAYE SCHIMMELBUSCH
Seattle, Washington

HUMAN hypersensitivity to air-borne non-pathogenic mold spores has been established as one cause of respiratory tract allergy in several parts of the United States. In the Pacific Northwest, certain asthmatic patients have variations in their symptoms suggesting mold-sensitivity, but frequently

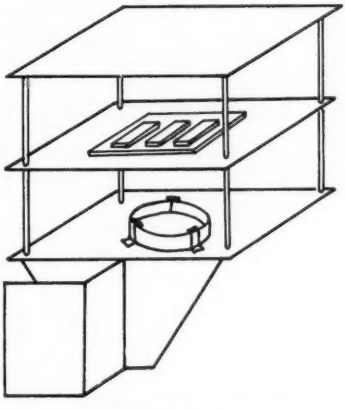

Fig. 1. Mold spore collection device.

no clear association can be established with mold species of importance elsewhere.[1] Accordingly, we have made daily mold spore counts simultaneously in both Tacoma and Seattle, Washington. The nature of the spores has been determined by exposing culture plates and identifying the species of the resulting colonies and their relative proportion.

From the Division of Allergy, Department of Medicine, University of Washington School of Medicine, Seattle, Washington.

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Dr. Colen is Clinical Instructor in Medicine and Dr. VanArsdel is Assistant Professor of Medicine and Head, Division of Allergy, University of Washington School of Medicine.

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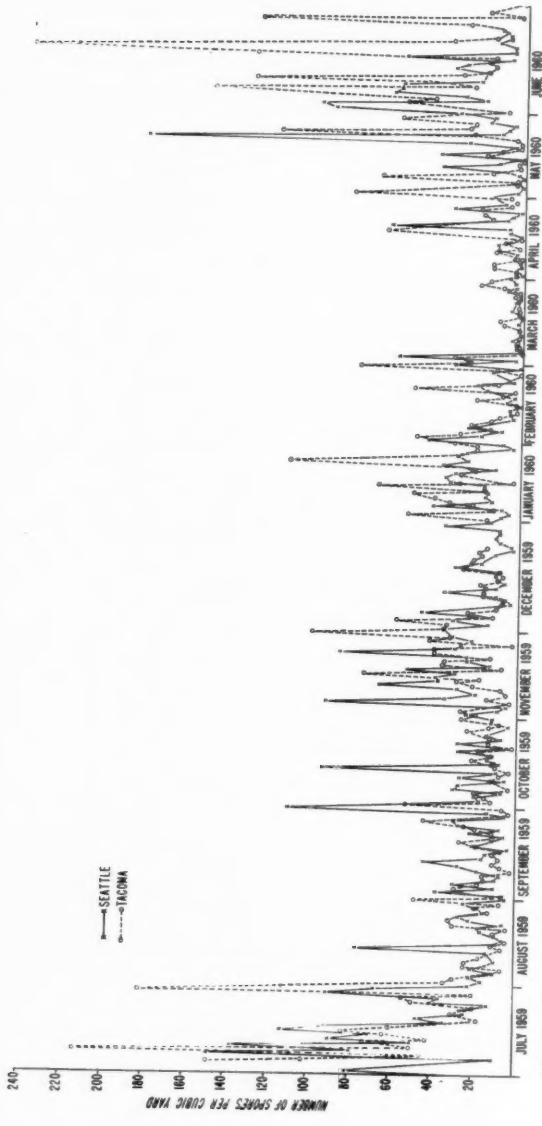

Fig. 2. Comparative total mold spore counts in Seattle and Tacoma, Washington, July 1959 through June 1960.

MATERIALS AND METHODS

For culturing molds, we have employed a modified malt agar* which consists of the following ingredients:

Difco malt extract	20	gm.
Peptone	10	gm.
KNO_3	0.5	gm.
Difco yeast extract	263	gm.
KH_2PO_4	0.1	gm.
$MgSO_4$	0.1	gm.
$FeSO_4$	0.05	gm.
USP Thiamine hydrochloride	0.1	gm.
Bacto agar	20	gm.
Distilled water to make	1000	ml.

We chose this rich medium in order to facilitate detection of as many species as possible.

Figure 1 shows our modification of the Durham pollen-collecting device,[2] which was used for simultaneous exposure of both culture plates and slides. One device was placed on the Health Sciences Building of the University of Washington in Seattle, and the other on the Medical Arts Building in Tacoma. Since variations in such factors as height and exposure or protection from prevailing winds failed to reveal any significant differences in either quantitative or qualitative botanical findings, the devices were placed arbitrarily in the most convenient available locations.

Culture plates have been exposed both indoors and outdoors during the past two and a half years, with microscopic identification of all representative mold colonies. Indoor exposures of duplicate plates for one hour were carried out in the homes of fifty-eight patients and seventeen non-allergic volunteers in diverse areas of both cities. Slides coated with petrolatum jelly have been exposed outdoors for twenty-four hours daily in both Tacoma and Seattle for more than two years and were exposed indoors also during the initial phase of this study. The spores were counted and their concentration per cubic yard of air calculated according to the procedure recommended by the pollen and mold committee of the American Academy of Allergy.[3] All slides were stained with 20 per cent NaOH for direct identification and Lactophenol Blue for preservation purposes.

Attempts were made to improve collection efficiency by covering the agar of some plates with a thin layer of mineral oil, and by varying exposure time for the culture plates from five minutes to twenty-four hours.

RESULTS

Figures 2 and 3 show the daily variation in spore counts for Seattle and Tacoma. Although the highest counts were found from May through October, the seasonal patterns were not as clear as in other parts of the

*We gratefully acknowledge the cooperation of Dr. Daniel E. Stuntz, Professor of Botany, University of Washington, who kindly suggested this culture medium, and gave valuable advice in mold identification.

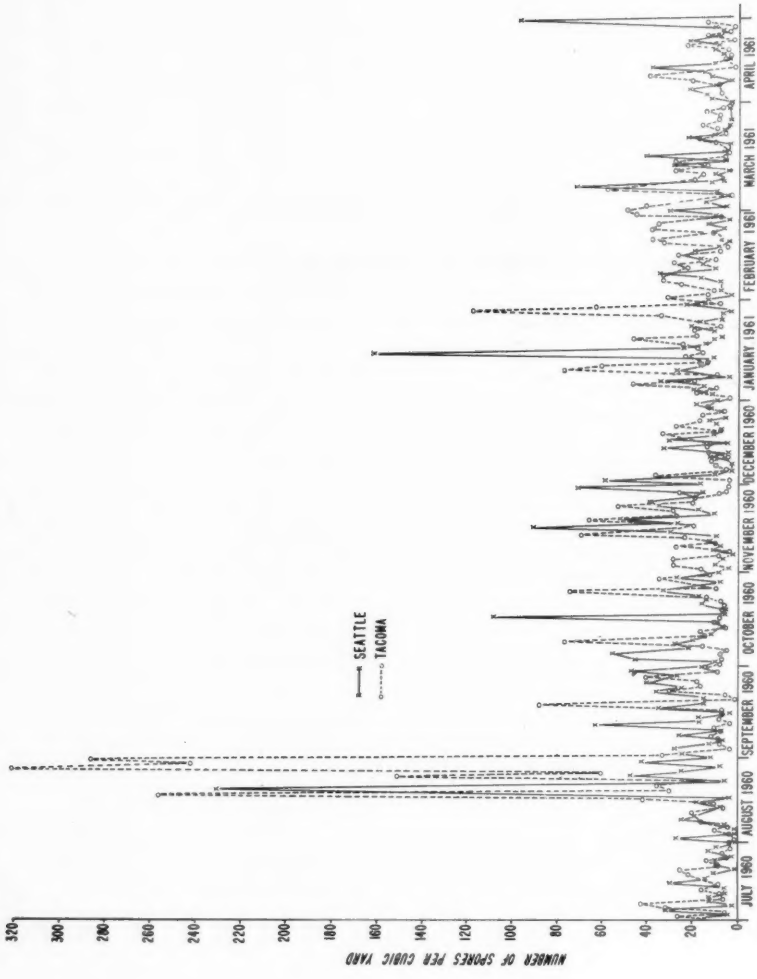

Fig. 3. Comparative total mold spore counts in Seattle and Tacoma, Washington, July 1960 through April 1961.

TABLE I. MOLD SPECIES FOUND INDOORS

Species	Jan.-Sept. '59		Oct. '59-July '60		Aug. '60-May '61		Total	
	N	%	N	%	N	%	N	%
Aspergillus	52	23.5	28	28.9	22	55.0	102	28.8
Penicillium	50	23.0	28	28.9	13	32.5	91	25.6
Cladosporium	45	20.6	4	4.1	0	—	49	13.8
Verticillium	22	10.1	11	11.3	0	—	33	9.3
Helminthosporium	14	6.5	5	5.2	1	—	20	5.6
Monascus	8	3.7	0	—	0	—	8	2.3
Scopulariopsis	0	—	5	5.2	1	—	6	1.7
Sporotrichum	4	1.8	2	2.1	0	—	6	1.7
Fusarium	5	2.3	0	—	0	—	5	1.4
Mucor	4	1.8	1	—	0	—	5	1.4
Cephalothecium	3	1.4	1	—	0	—	4	1.1
Alternaria	1	—	1	—	1	—	3	0.8
Paecilomyces	3	1.4	0	—	0	—	3	0.8
Cephalosporium	2	0.9	1	—	0	—	3	0.8
Botryosporium	0	—	3	3.1	0	—	3	0.8
Aleurisma	—	—	2	2.1	1	—	3	0.8
Gliocladium	2	0.9	0	—	0	—	2	0.6
Neurospora	2	0.9	0	—	0	—	2	0.6
Stemphylium	1	0.5	0	—	0	—	1	—
Pullularia	0	—	1	—	0	—	1	—
Phoma	0	—	1	—	0	—	1	—
Syncephalastrum	0	—	1	—	0	—	1	—
Dicoccum	0	—	1	—	0	—	1	—
Rhizoctonia	0	—	1	—	0	—	1	—
Trichothecium roseum	0	—	0	—	1	—	1	—
Total colonies	218		97		40		355	

United States. Table I shows the mold species found on indoor exposures of culture plates. Table II shows the same for mold species found outdoors. These studies indicated that the distribution of mold species in the home generally was parallel to that found outdoors in regard to the five most common species. Aspergillus and Penicillium were by far the most common in this area. Hormodendron (Cladosporium) was found much less frequently than elsewhere, whereas Alternaria was practically absent. In no

TABLE II. MOLD SPECIES FOUND OUTDOORS

Species	Jan.-Sept. '59		Oct. '59-July '60		Aug. '60-May '61		Total	
	N	%	N	%	N	%	N	%
Aspergillus	26	35.6	115	46.4	194	51.3	335	48.0
Penicillium	15	20.6	68	27.4	117	31.0	200	28.6
Verticillium	14	19.2	16	6.4	14	3.7	44	6.3
Cladosporium	7	9.6	8	3.2	18	4.8	33	4.7
Helminthosporium	7	9.6	7	2.9	9	2.4	23	3.3
Scopulariopsis	2	2.7	7	2.9	1	—	10	1.4
Aleurisma	0	—	1	—	8	2.1	9	1.3
Paecilomyces	0	—	2	0.8	6	1.6	8	1.1
Fusarium	0	—	5	2.0	1	—	6	0.9
Botrytis	0	—	4	1.6	1	—	5	0.7
Trichothecium roseum	0	—	2	0.8	2	0.5	4	0.6
Sporotrichum	0	—	2	0.8	2	0.5	4	0.6
Zygorhyncus	0	—	2	0.8	1	—	3	0.4
Alternaria	1	—	1	—	0	—	2	0.3
Trichoderma	0	—	2	0.8	0	—	2	0.3
Botryosporium	0	—	1	—	1	—	2	0.3
Rhizopus	0	—	1	—	1	—	2	0.3
Thielaviopsis	0	—	0	—	2	0.5	2	0.3
Mucor	1	—	0	—	0	—	1	—
Syncephalastrum	0	—	1	—	0	—	1	—
Neurospora	0	—	1	—	0	—	1	—
Pythium	0	—	1	—	0	—	1	—
Trichosporium	0	—	1	—	0	—	1	—
Total colonies	73		248		378		699	

single home did we find an unusually high concentration of any of the less common mold species.

A comparison between plain culture plates and plates on which the medium was covered by means of a thin layer of mineral oil showed no

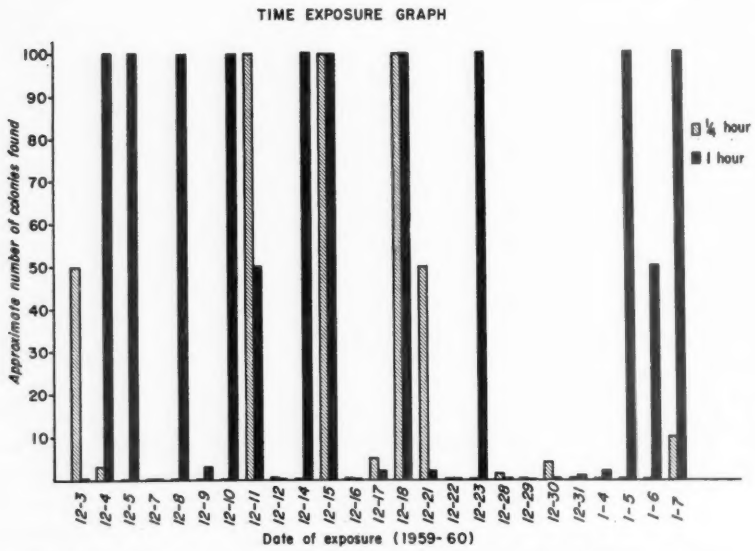

Fig. 4. Number of colonies recovered on mold culture plates; 15-minute exposure compared with 1-hour exposure.

significant difference in number of colonies obtained. The usual time of exposure (between two and twelve minutes) appeared insufficient in the Puget Sound area. For indoor studies the optimum time for exposure ranged between one and four hours, but no advantage was gained by exposure for more than one hour. In regard to outdoor exposures, we have attempted to relate the number of colonies per plate with the various lengths of exposure, by means of exposing different plates for various lengths of time. Figure 4 shows one phase of this study. Although occasionally the fifteen minute colony counts were higher than the one hour counts, generally the one hour counts appeared to be optimal for our purpose.

There was no marked difference between the number of spores found upon indoor and outdoor slide exposure (Fig. 5).

DISCUSSION

This is primarily a report of the botanical findings in the Puget Sound area, so we shall attempt no analysis of the associated clinical observations.

The fluctuations in spore counts correlated well with the seasonal variation in asthmatic symptoms of those patients who had clear-cut specific skin sensitivity to mold antigens.

In order to establish the clinical association more adequately, we are

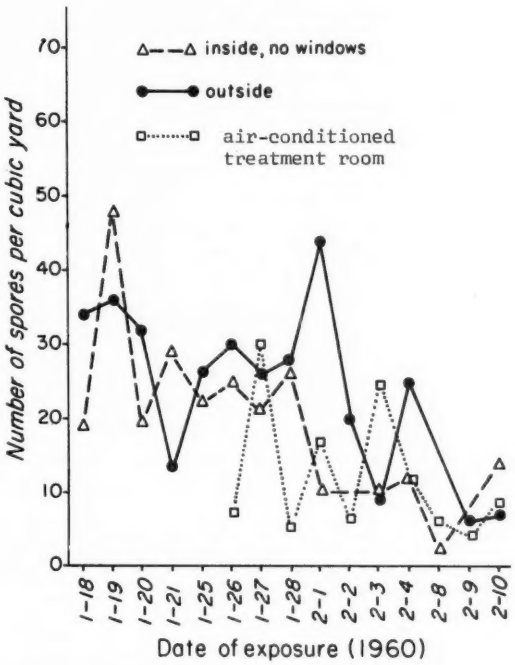

Fig. 5. Comparison of inside and outside spore counts.

now carrying out procedures for experimental reproduction of symptoms in selected hypersensitive patients. Whether Aspergillus and Penicillium spores are as important in the pathogenesis of asthma as their prevalence in this area suggests is not yet established. Certain of the less common molds may be clinically significant in patients with strong hypersensitivity to them, but would be relatively unimportant in terms of prevalence and distribution alone.

In England, the prevalence of Aspergillus and Penicillium is also relatively high, particularly in urban areas, but Cladosporium is by far the most common.[4] Our findings are quite unique when compared with published reports from several other parts of the world.[5-8] The effect of local climatic conditions on mold spore counts in the Puget Sound area is a matter of considerable interest to us, but we are deferring any systematic evaluation until data are collected over a longer period of time.

ACKNOWLEDGMENTS

We are indebted to Dr. Lois Frayser, Clinical Assistant Professor of Medicine and Dr. James E. Stroh, Clinical Associate Professor of Medicine, University of Washington, for helpful advice on many occasions.

SUMMARY

Daily mold spore counts in both Seattle and Tacoma, Washington, have been performed for approximately two years and the nature of the spores determined by exposing culture plates and identifying the species and relative proportion of the resulting colonies. Over a two and a half year period, the predominant mold species found on outdoor exposures have included: Aspergillus (48 per cent), Penicillium (29 per cent), Verticillium (6 per cent), Cladosporium (Hormodendron) (5 per cent), and Helminthosporium (3 per cent). The proportion of mold species found in 75 different homes was quite similar. This distribution of species differs markedly from those reported from other geographical areas.

Mold spore counts are highest from May through October, but the seasonal patterns are less clear-cut than in other parts of the United States. Fluctuations are clear-cut, occurring at the same time in both cities.

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1207 Medical Arts Bldg. (Dr. Colen)
Tacoma, Washington

KOCH INOCULATES FOUR GUINEA PIGS; TWO CONTROLS

In order that our procedures should be rewarded by a positive result, the conditions existing in nature must be adhered to as closely as possible, a precaution which was neglected in the early days of experimental research into infectious diseases. People have experimentally endeavoured in the most primitive way to communicate to dogs, cats, rabbits, guinea pigs and the like, diseases which have hitherto only been observed in man. Experience has, however, taught us that it is not a matter of indifference what species of animal is employed for the experiment, and that the method by which the inoculation is performed has the greatest influence on the success of the experiment.—ROBERT KOCH, *On the Investigation of Pathogenic Organisms,* trans., VICTOR HORSELY, in *Recent Essays on Bacteria in Relation to Disease,* 1886.

THE CORRELATION BETWEEN SKIN AND RESPIRATORY MUCOUS MEMBRANE TESTS WITH MOLDS IN ALLERGIC RHINITIS

SALMON R. HALPERN, Ph.D., M.D., F.A.C.A., JAMES HOLMAN, M.D., and CHARLES WHITTAKER, M.D.

Dallas, Texas

ALLERGISTS are generally agreed that positive skin tests to molds do not necessarily indicate clinical sensitivity. A clinical history to confirm the skin tests is highly desirable and in many areas of the country this is not difficult to obtain. However, in the Southwest, the seasons greatly overlap. Molds are found almost the year around, and often at the height of the mold season many different kinds of pollen are also prevalent.

For a long time, the authors have been concerned by the fact that a large number of people, children more so than adults, exhibited positive skin reactions to molds (Table I). The clinical significance of this was not always clear, since the history was often of no assistance in judging the patient's sensitivity. This study was undertaken to determine the incidence of clinical sensitivity to molds, by the nasal provocative test, in patients with perennial allergic rhinitis. We also were desirous of comparing three preparations of alternaria tenuis which were extracted by different processes.

TABLE I. PER CENT OF POSITIVE SKIN TESTS IN CHILDREN WITH RESPIRATORY ALLERGY

Number	Pollens	Dust	Molds	Foods
278	79%	88%	85%	79%

REVIEW OF LITERATURE

The earliest record of a provocative nasal test was made in 1835, when Kirkman[1] sniffed sweet vernal grass and induced a severe attack of hay fever. Blackley,[1] in 1873, tested various pollens by conjunctival, nasal, and buccal instillation and carried out the first systematic study of hypersensitivity. Dunbar,[1] in 1903, while placing considerable reliance on conjunctival tests, also believed that nasal tests were valuable. Skin tests were not commonly used until 1907.

The literature has been reviewed, and those papers in which the data are sufficiently recorded have been summarized in Tables II and III.

From the Departments of Pediatrics and Pharmacology, the University of Texas Southwestern Medical School, and the Department of Allergy, Children's Medical Center, Dallas, Texas.

Presented at the scientific meeting of the Association of Allergists for Mycological Investigations, Dallas, Texas, March 14, 1961.

MATERIAL AND METHODS

There were 146 patients in this study, about equally divided between clinic and private patients. Forty were adults and the others were between the ages of two and fifteen years. Ninety had perennial allergic rhinitis,

TABLE II. PROVOCATIVE INTRANASAL TESTS WITH VARIOUS INHALANTS IN PATIENTS WITH ALLERGIC RHINITIS WHO HAD POSITIVE SKIN TESTS TO THESE INHALANTS

1930-1939

Author	Inhalant	Number	Positive	Negative
Efron & Penfound (1930)	Ragweed	32	25 (80%)	7 (20%)
	Cocklebur	14	3 (21%)	11 (79%)
	Marsh elder	16	0	16 (100%)
Blumstein, G (1937)	Timothy	65	27 (42%)	38 (58%)
	Plantain	52	10 (19%)	42 (81%)
	Ragweed	83	67 (81%)	16 (19%)
	Trees	29	4 (14%)	25 (86%)
Harris, L. (1939)	Grain dust	5	4 (80%)	1 (20%)
	Grain smut	5	3 (60%)	2 (40%)
Total		301	143 (48%)	158 (52%)

1940-1945

Author	Inhalant	Number	Positive	Negative
Chobot et al. (1940)	Molds	12	12 (100%)	0
Harris, L. (1940)	Alternaria	29	11 (38%)	18 (62%)
Blumstein, G. (1945)	Alternaria	41	10 (24%)	31 (76%)
	Hormodendrum	25	5 (20%)	20 (80%)
	Monilia	33	3 (9%)	30 (91%)
	Helminthosporum	26	2 (7%)	24 (93%)
	Mucor	40	1 (3%)	39 (97%)
	Other molds	179	0	179 (100%)
Total		385	44 (11%)	341 (89%)

TABLE III. PROVOCATIVE BRONCHIAL TESTS WITH VARIOUS INHALANTS IN ASTHMATIC PATIENTS WHO HAD POSITIVE SKIN TESTS TO THESE INHALANTS

Author	Inhalant	Number	Positive	Negative
Stevens, F. (1934)	Various	34	15 (44%)	19 (56%)
Harris, L. (1940)	Alternaria	22	11 (50%)	11 (50%)
Citron et al. (1958)	Grass	19	18 (94%)	1 (6%)
Schiller & Lowell (1952)	House dust	65	43 (66%)	22 (34%)
	Ragweed	57	22 (39%)	35 (61%)
	Birch	16	5 (31%)	11 (69%)
	Oak	13	3 (23%)	10 (77%)
	Timothy	28	3 (11%)	25 (89%)
	Alternaria	20	3 (15%)	17 (85%)
	Hormodendrum	14	3 (21%)	11 (79%)
Total		288	126 (43%)	162 (57%)

forty-three had asthma and perennial allergic rhinitis, and thirteen had only asthma. One hundred and one had no previous hyposensitization. Thirty-three patients with perennial allergic rhinitis who had negative skin tests to molds served as controls. One hundred and twenty-six patients with positive skin reactions to molds were given nasal tests, using 5 per cent

glycerine in normal saline without added mold antigen prior to the provocative tests.

The material used for the skin and provocative nasal tests was from the following sources:

1. Stock solution: The dried powder of alternaria tenuis was obtained from three reliable commercial sources. It was extracted in Stier's solution and made up in a concentration of 1:50.

TABLE IV. PROVOCATIVE INTRANASAL TESTS WITH ALTERNARIA TENUIS (STOCK) IN PATIENTS WITH PERENNIAL ALLERGIC RHINITIS WHO HAD POSITIVE SKIN TESTS TO ALTERNARIA

Skin Tests	Number	Intranasal Tests		
		Positive	Equivocal	Negative
Scratch	14	8 (57%)	3 (21%)	3 (21%)
I.D.	40	15 (37.5%)	6 (15%)	19 (48%)
Total	54	23 (43%)	9 (16%)	22 (41%)

2. Alternaria type 33 in the concentration of 1:100 was obtained from Hollister-Stier.

3. Alternaria MMP in the concentration of 1:50 was obtained from the Association of Allergists for Mycological Investigations.[21]

Scratch tests were first done. If these were equivocal or negative, intradermal testing was performed in the following way: the stock solution was in a concentration of 1:250; type 33 and MMP were in the concentration of 1:1000. In provocative tests, the various preparations of alternaria were made up in a concentration of 1:1000 of 5 per cent glycerine in normal saline. The material was sprayed into the nose under direct vision using either a tuberculin syringe attached to a 25-gauge needle or a DeVilbiss nebulizer. With the syringe, about 0.5 ml. was used, and with the nebulizer, about 0.05 ml. was used.

The criteria for determining whether a test was positive were the findings of any two of the following: sneezing, excessive secretions, swelling of the turbinates, and pruritus of the nose and throat.

Other molds were used for provocative tests in the same manner as described for alternaria. These were either of the stock or type 33 variety.

As a rule, the patients were asymptomatic. A few had moderately boggy mucous membranes. A number of patients had both skin and nasal tests to different extracts of alternaria tenuis as well as to various other molds.

RESULTS

The tables summarize the results of the provocative tests. When Tables IV, V, and VI are compared, it will be noted that the extract of alternaria

supplied by the Association of Allergists for Mycological Investigations (MMP) gave the greatest number of positive scratch reactions and also the highest per cent correlation. It was followed by type 33 and the stock solution.

TABLE V. PROVOCATIVE INTRANASAL TESTS WITH ALTERNARIA TENUIS (TYPE 33) IN PATIENTS WITH PERENNIAL ALLERGIC RHINITIS WHO HAD POSITIVE SKIN TESTS TO ALTERNARIA

Skin Tests	Number	Intranasal Tests		
		Positive	Equivocal	Negative
Scratch	36	22 (61%)	3 (8%)	11 (31%)
I.D.	11	4 (36%)	0	7 (64%)
Total	47	26 (56%)	3 (8%)	18 (38%)

In Table VII, type 33 was contrasted with MMP in the same patients, and the difference is again in favor of MMP extract.

Table VIII demonstrates that in using type 33 no correlation existed between positive skin tests and a nasal test in asthmatic patients. However, with MMP in four patients, a positive correlation appeared. At this point in our study, our supply of MMP was exhausted. This obviously requires further study.

TABLE VI. PROVOCATIVE INTRANASAL TESTS WITH ALTERNARIA TENUIS (MMP) IN PATIENTS WITH PERENNIAL ALLERGIC RHINITIS WHO HAD POSITIVE SKIN TESTS TO ALTERNARIA

Skin Tests	Number	Intranasal Tests		
		Positive	Equivocal	Negative
Scratch	55	37 (67%)	0	18 (33%)
I.D.	5	1 (20%)	0	4 (80%)
Total	60	38 (63%)	0	21 (37%)

Glycero-saline without the added antigen was used as the control solution. In 126 patients, there were two positive reactions.

Thirty-three patients who had perennial allergic rhinitis, but negative skin reactions to type 33 alternaria, were subjected to nasal testing. Only one gave a positive reaction.

DISCUSSION

When skin tests cannot be confirmed by the history, provocative testing may be extremely helpful to the clinician in deciding what antigens are required for hyposensitization. Urbach[11] stated: "A negative nasal test along with a positive skin test strongly indicates that the test substance is not to be considered responsible for nasal allergy." He then went on to

say: "We find nasal tests almost always reliable in their application to hay fever patients." Many others have confirmed Urbach's observations.[12-15]

Damgaard[16] found that 80 per cent of asthmatic children showed a positive correlation between the history and the provocative tests. The

TABLE VII. COMPARISON OF PROVOCATIVE NASAL TESTS BETWEEN ALTERNARIA TENUIS (TYPE 33) AND MMP IN PATIENTS WITH PERENNIAL ALLERGIC RHINITIS WHO HAD POSITIVE SKIN TESTS TO ALTERNARIA

Skin Tests	Number	Intranasal Tests		
		Positive	Equivocal	Negative
Scratch (33)	22	13 (59%)	0	9 (41%)
Scratch (MMP)	30	20 (67%)	0	10 (33%)
I.D. (33)	8	3 (37.5%)	0	5 (62.5%)

positive provocative tests closely paralleled the degree of skin reactivity. Stevens[8] observed that asthmatic patients showed a definite correlation between dermal and pulmonary sensitivity. Our results are in close agreement with the findings of Damgaard and Stevens, in that those patients who had positive scratch tests also showed a better correlation with the nasal tests.

TABLE VIII. PROVOCATIVE INTRANASAL TESTS WITH ALTERNARIA TENUIS IN 13 PATIENTS WITH ASTHMA WHO HAD POSITIVE SKIN TESTS TO ALTERNARIA

Skin Tests		Number	Intranasal Tests		
			Positive	Equivocal	Negative
Scratch	Type 33	9	0	1 (11%)	8 (89%)
	MMP	4	4 (100%)	0	0
I.D.	Type 33	3	1 (33%)	0	2 (67%)
Total		16	5 (39%)	1 (7%)	10 (62%)

Provocative tests have been reported to show decreased sensitivity with treatment. Feinberg[17] found in an equal number of treated and untreated patients with ragweed pollinosis that the treated group showed a lessened sensitivity. Rysing,[18] testing asthmatic children before and after treatment with house dust, recorded a definitely increased tolerance following hyposensitization. Citron[9] stated that in grass-sensitive patients decreased inhalation sensitivity occurred following treatment. In our series, 101 patients had no previous treatment. These showed essentially the same response as the treated patients to the provocative testing. However, tests were not done with different concentrations which may well account for these differences.

Colldahl,[19] in 1952, found that, in spite of statements to the contrary, a reliable bronchial test could be performed on an asthmatic patient when

his chest was not entirely clear. He observed a positive test in 46 per cent of 108 subjects when they had "roughened breath sounds" and in 48 per cent of sixty-one asymptomatic patients. Feinberg[17] cited two instances in which sensitivity was increased during periods of discomfort. In some of our children, there was a moderate degree of rhinitis at the time of testing. This did not appear to alter the results in that negative as well as positive reactions were observed. Tuft[20] stated that nasal testing could not be performed on a patient whose nose was already blocked, nor could it be done if the nasal mucous membranes were hyperirritable. We believe this is true and in our patients who had marked difficulties, testing was not done.

On a few occasions, we noted that the opposite side of the nose would become edematous and watery. We have no explanation for this other than to suppose that this is a simple reflex phenomenon.

Feinberg[17] stated that different test results occurred in the same patient, depending on his clinical state. Testing with ragweed pollen bronchially and intranasally, he was able to demonstrate greater reactivity of the mucous membranes in a house dust- and ragweed-sensitive patient at a time when house dust was producing symptoms. He also obtained increased provocative reactions in a patient following a severe episode of infectious bronchitis.

It has been extremely difficult to compare our findings with the previously cited studies, because frequently no definite diagnosis was recorded and no standardized method of testing was used; sprays of various concentrations were used, dry powder was insufflated, or prolonged applications of solutions were made.

It is interesting to note that the most commonly found mold in our area, namely alternaria, gave the highest degree of correlation between scratch and nasal tests. The molds found less frequently, but which nevertheless gave large skin reactions, almost universally showed very poor to no correlation with the provocative test (Table IX). This occurred if the application of the mold was in the form of dry powder or in solution. There are indeed exceptions to this generalization.

CASE REPORT

C.P., a white male child, three years and five months old, with history of asthma since one year of age, lived in a house which sweated a great deal. His bedroom walls had considerable mildew. Skin tests showed positive reactions to elm, feathers, dust, with the scratch test method, and a 1+ intradermal test to aspergillus. All other mold tests were negative. A mold plate was exposed in his room and aspergillus grew out. Nasal tests to alternaria and aspergillus showed only a positive result with aspergillus.

Our results suggest that about two-thirds of the patients with allergic rhinitis who have positive skin tests to alternaria are probably clinically sensitive to it as determined by the nasal test. We should like to stress the point that it is conceivable that the concentration of mold used in the provocative tests is considerably greater than that which the individual will ever encounter in his environment.

Hence, he may have a positive skin and nasal test and never have allergic rhinitis due to the mold in question unless unusual circumstances produce a very great exposure. In patients with perennial allergic rhinitis, in whom the diagnosis of mold allergy is difficult, or in whom the desensitizing therapy is unsatisfactory, nasal tests appear to be of great assistance in the understanding and treatment of their symptoms.

MMP appears to be superior to type 33 and the stock preparation as judged by the larger skin reactions and the greater correlation with the nasal provocative tests.

TABLE IX. PROVOCATIVE INTRANASAL TESTS WITH OTHER MOLDS IN PATIENTS WITH PERENNIAL ALLERGIC RHINITIS WHO HAD POSITIVE SKIN TESTS TO THESE MOLDS

Mold	Scratch	I.D.	Total	Intranasa lTests		
				Pos.	Equiv.	Neg.
Hormodendrum	1	19	20	5 (25%)	7 (35%)	8 (40%)
Helminthosporum	8	8	16	9 (56%)	0	7 (44%)
Spondylocladium	3	4	7	0	0	7 (100%)
Rhizopus	1	6	7	0	0	7 (100%)
Penicillium	0	9	9	2 (22%)	1 (11%)	6 (67%)
Aspergillus	2	9	11	1 (9%)	2 (18%)	8 (73%)
Monilia	2	9	11	3 (27%)	3 (27%)	5 (46%)
Fusarium	1	8	9	0	0	9 (100%)
Cephalosporum	1	6	7	0	0	7 (100%)
Total	19	77	96	19 (20%)	13 (14%)	64 (66%)

SUMMARY

1. One hundred and forty-six patients (forty adults and 106 children), with allergic rhinitis, who had positive skin tests to molds, were subjected to nasal provocative tests to determine their clinical sensitivity to molds.

2. Three different preparations of alternaria tenuis (stock, type 33, and MMP) were compared.

3. The provocative tests were performed by spraying the nasal mucous membranes with a 1:1000 glycero-saline solution.

4. The stock solution showed 43 per cent; type 33, 56 per cent, and MMP, 63 per cent correlation between dermal and nasal tests. Thus, approximately two-thirds of patients with positive skin tests to alternaria tenuis were clinically sensitive to this mold, using the nasal test as a criterion. An even greater correlation was noted in patients with a positive scratch test.

5. With such molds as spondylocladium, fusarium, penicillium, aspergillus, cephalosporium, and rhizopus, in spite of large skin reactions, the correlation was very poor to none. Hormodendrum and helminthosporum fell between the latter group and alternaria.

6. The MMP preparation of alternaria appears to be a superior antigen as judged by the stronger skin reactions and the higher degree of correlation between skin and nasal tests.

7. In patients suspected of having allergic rhinitis due to molds, nasal provocative testing may be of great assistance in the diagnosis and management of their symptoms.

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3534 Maple Avenue

LAWS OF NATURE

The pre-occupation of science is then the search for simple statements which in their joint effect will express everything of interest concerning the observed recurrences. This is the whole tale of science, that and nothing more. It is the great Positivist doctrine, largely developed in the first half of the nineteenth century, and ever since growing in influence. It tells us to keep to things observed, and to describe them as simply as we can. This is all we can know. Laws are statements of observed facts. This doctrine dates back to Epicurus, and embodies his appeal to the plain man, away from metaphysics and mathematics. The observed facts of clear experience are understandable, and nothing else. Also "understanding" means "simplicity of description."—Alfred North Whitehead, *Adventures of Ideas,* The New American Library, 1955.

USE OF BUCCAL PROTEASE THERAPY IN CHRONIC BRONCHIAL ASTHMA

DONALD B. FRANKEL, M.S., M.D., F.A.C.A.,
ABE L. AARONSON, M.D., F.A.C.A., and
NORMAN J. EHRLICH, M.D., F.A.C.A.

Chicago, Illinois

PRELIMINARY findings[1] on the use of buccal protease* in treatment of chronic "intrinsic" asthma were sufficiently encouraging to warrant further investigation. An elaborate and controlled study was devised to appraise this form of therapy more accurately. The results, which are reported and discussed in this paper, seem to substantiate earlier tentative conclusions.

NATURE OF ASTHMA

The terms "extrinsic" and "intrinsic" serve a descriptive purpose when applied to allergic bronchial asthma, in spite of the confusion sometimes provoked. Lowell[2] states that bronchial asthma in older patients is composed of both elements: "extrinsic," that caused by inhaled allergens, and "intrinsic," a reactivity to nonspecific factors. Knowles[3] describes intrinsic asthma as a chronic smoldering process, never completely symptom-free and punctuated by severe bronchospastic episodes, usually associated with acute infection or acute exacerbations of a chronic infection. Infection adds to the functional defect by maintaining bronchospasm, and by promoting excess secretions which lead to further hinderance of air flow.

Cooke[4] indicates that asthma may be caused by infection alone or in combination with other intrinsic factors. He lists *Staphylococcus aureus* as one of the organisms most persistently encountered. Many other workers, such as Woodward,[5] Prissick,[6] Stiles and Chapman[7] found that *Staphylococcus aureus* was the most common pathogen present in respiratory tract infections. Baker[8] confirmed this, noting that others such as *Streptococcus, Hemophilus influenzae* and *Pneumococcus* were more seasonal pathogens. Cherniak et al[9] conducted a controlled study on the effects of long-term antibiotic therapy in patients with chronic bronchitis and bronchiectasis which indicated the benefits gained by partial if not complete destruction of the pathogenic bacterial flora of the respiratory tract in such conditions. Zinsser[10] theorized that a hypersensitive state must be suspected in all subacute and chronic staphylococcal infections regardless of the site of disease.

Dr. Frankel is Clinical Instructor, Chicago Medical School; staff member, Mt. Sinai Hospital Allergy Clinic.
Dr. Aaronson is Chief, Mt. Sinai Allergy Clinic; Head, Allergy Department, Chicago Medical School.
Dr. Ehrlich is Associate Professor, University of Illinois Medical School; staff member, Allergy Clinic, Illinois Research Hospital; Attending Physician, Michael Reese Hospital.

*Supplied as Varidase® Buccal Tablets, Lederle Laboratories, Pearl River, New York.

The findings of these and many other investigators seemed to indicate that chronic bronchial asthma in older patients was composed partially of an intrinsic (infectious) component. Of course, there are many studies which confirm the existence of extrinsic components (pollens, molds, feathers, pets, et cetera) in many of these patients.[8,9] Blumstein[11] states that the "cure" of bronchial asthma lies in its prevention. Prevention becomes possible only when *every* factor which influences the course of the disease is known and can be controlled.

Thus, this study was designed in an attempt to show that further lung destruction in the older chronic bronchial asthmatic patient may be prevented by eliminating the chronic infection that consistently triggers the pathology. Shaffer et al[12] state that broad spectrum antibiotics, rotated over long periods of time, may offer these patients some relief. However, antimicrobial agents—penicillin, sulfonamides, etc., alone or in combination—have only temporary effect. The study reported here evaluates the role of buccal protease, as an adjunctive agent, in the prolongation and maintenance of this relief.

RATIONALE FOR BUCCAL PROTEASE THERAPY

The early stage of an inflammatory process is marked by local vasodilatation, increased capillary permeability, and leukocytic migration to the damaged area. These changes are followed by swelling of capillary endothelium, gradual slowing down of circulation, formation of highly polymerized particles of microthrombi through fibrin clotting, and clumping of leukocytes. Abnormal metabolism in the involved tissues results from changes such as vigorous glycolysis, lactic acid accumulation, increased carbon dioxide tension, decreased oxygen tension, and potassium concentration. The stasis is further intensified by impairment of connective tissue permeability through fibrin formation, edema, thickening of the exudate, as well as the resultant release of desoxyribonucleoprotein from cellular debris.

This local action "walls off" the causative factor from the rest of the body and, in effect, isolates the necrotic process. The "walling off" interferes with the normal reparative processes and prevents most exogenous and endogenous therapeutic agents from reaching the involved area.

The ability to reverse this inflammatory situation is dependent upon the proteolytic enzyme system of the body. Fibrinolysis is established by kinase activation of plasminogen to form plasmin. The dissolution of fibrin thins the exudate and increases the tissue and capillary permeability. Thus the primary reactions of inflammation are re-established; increase in blood flow, leukocyte migration, and capillary permeability allow the body to reduce and gradually eliminate inflammation.

Obviously, there is need for exogenous therapy which would increase local anti-inflammatory activity by accelerating the plasminogen-plasmin system. More rapid fibrinolysis would facilitate access of antimicrobial agents to infectious and necrotic areas. More successful penetration of

exogenous and endogenous substances would greatly alleviate the condition in patients with chronic intrinsic or combined intrinsic and extrinsic asthma.

METHOD

Buccal protease was used because it is easily administered and convenient to patients. Innerfield[13] has shown that streptokinase accelerates the normal process of lysis and increases the anti-inflammatory process. The Ouchterlony gel diffusion technique indicates that buccally administered streptokinase penetrates mucosa and gains access to the blood stream.[14]

TABLE I. ASTHMATIC PATIENTS SELECTED FOR TEST
Total—Fifty-one

Age			State of Disease		Duration of Disease		
35-42	43-50	51-69	Severe	Moderate	3-5 Years	6-10 Years	Over 10 Years
7	25	19	31	20	5	28	18

This study includes the period from February, 1959, through December, 1960. The fifty-one patients selected met the following criteria: (1) they were over thirty-five years old; (2) were thoroughly examined and evaluated; (3) had a history of chronic bronchial asthma for at least three years; (4) were receiving hyposensitization therapy; (5) continued to receive adjunctive or regular medication (Table I).

TABLE II. COURSES OF THERAPY GIVEN

Group	Cumulative Totals		Number of Courses Per Patient					
			3 or less		4 or 5		6 or 7	
	Patients	Courses	Patients	Courses	Patients	Courses	Patients	Courses
A	16	43	3 7 2	3 2 1	2 2	4 5	0 0	0 0
B	13	46	2 4 1	3 2 1	1 3	4 5	2	6
C	17	73	3 3	2 3	4 3	4 5	3 1	7 6
D	14	51	3 4	2 3	3 3	4 5	1	6
Totals	60	213	32	73	21	95	7	45

A double-blind technique was used to evaluate results. The patients were divided into four dosage groups: (A) Antibiotic agents only—1 Gm/day for twenty-eight days; (B) Buccal protease only—10,000 U streptokinase and 2500 U streptodornase, four times a day for twenty-eight days; (C) Buccal protease as above—seven days, buccal protease plus antibiotic agents—seven to fourteen days, buccal protease alone—seven days; (D)

TABLE III. RESULTS

	Group A[1]			Group B[2]			Group C[3]			Group D[4]		
	Improved	Worse	No Change	Improved	Worse	No Change	Improved	Worse	No Change	Improved	Worse	No Change
Dyspnea	16	6	21	12	9	25	66	4	2	22	18	11
Cough	16	4	23	14	19	13	51	3	19	16	21	14
Number attacks	10	3	30	4	6	26	52	8	13	15	14	22
Ease of resolving attacks	4	4	35	3	6	37	27	6	40	16	19	16
Incidence of respiratory infections	22	1	20	10	5	35	64	1	8	9	7	35
General status	10	4	29	8	4	34	65	2	6	14	24	3
Sputum changes	15	9	19	14	16	16	59	3	11	14	9	28
Total	93	31	177	65	65	186	384	27	99	106	112	129

Group A[1]—Antibiotics only—1 Gm/day for 28 days.
Group B[2]—Buccal protease only—10,000 U streptokinase and 2500 U streptodornase, 4 times a day for 28 days.
Group C[3]—Buccal protease as above— 7 days, buccal protease plus antibiotics—7-14 days, buccal protease alone—7 days.
Group D[4]—Placebo regimen—simulated buccal protease and antibiotics as given to patients in group C.

Placebo regimen—simulated buccal protease and antibiotic agents as given to patients in group C. Each of these schedules constituted one "course" of therapy. Patients in all groups received up to seven courses during the period of evaluation, and some were placed in more than one group during the course of the study (Table II).

Respiratory function tests (maximal breathing capacity, vital capacity, and residual volumes) were done on some patients early in the study and again at the termination of therapy. Normal values were obtained from the treatises of Pappenheimer,[15] Spector,[16] and Baldwin.[17]

In addition, subjective impressions were obtained from responses to the following questions:

1. Do you take the same, more or less medication for relief?
2. Do you find relief is harder or easier or the same to accomplish with your usual medication?
3. Have you made more, less, or the same number of trips to the hospital or office for emergency relief of attacks?
4. Are you having more, less or the same number of asthmatic episodes?
5. Are you wheezing more, less or about the same amount?
6. Is the dyspnea less, more or the same on exertion (laughing, walking, working, et cetera)?
7. Do you cough more, less or the same?
8. Has the cough more, less or the same amount of productivity?
9. Is your general status better, worse or the same?

RESULTS

Table III demonstrates that short courses of antibiotic agents alone may have a temporary or mild effect on some patients. However, their effectiveness is generally minimal. When the administration of antibiotic agents was ceased, all patients rapidly reverted to their previous state of illness. Buccal protease alone, used for patients in group B, had even less effect on the general picture. However, those patients receiving three or four concurrent courses of buccal protease had less viscous, more easily expectorated sputum, cough was diminished, and dyspnea somewhat decreased. Moreover, there was a significant decrease in the severity of respiratory infections (Table III).

Group C patients, those who received buccal protease and antibiotic courses, showed remarkable differences from patients in each of the other groups. Improvement of general status and of all symptoms was evident. Most favorable results were observed in dyspnea, cough, frequency of attacks, and sputum changes. In some patients one course alone produced readily apparent changes.

Significant variances in the effect of medication upon sputum were observed among the four groups. In group C, the sputum of all but two patients (among those who received only two courses of therapy) changed

from yellow to white, and remained so for many weeks. Similar changes were noted in only one-third of those patients in group A and 15 per cent in group B. However, in group B, the sputum was less viscous and more easily expectorated in approximately 30 per cent of the patients. Some patients in this group also complained of excessively copious sputum, but this we felt to be an improvement. There were no changes in sputum color in patients who received the placebo regimen, although some claimed an improvement in viscosity and volume.

Data in Table III and in Figure 1 indicate a direct relationship between length of treatment with protease and antibiotics (group C) and favorable results. Patients in this group, who received four or more courses, had significantly decreased dyspnea, cough, and incidence of attacks. Respiratory infections decreased, not only in incidence but in severity as well. Sputum change was especially pronounced, in that after four courses, it changed from yellow to white, was more easily expectorated and decreased in amount. Improvement in general status was excellent. Mental improvement could be attributed directly to the fact that the patients ate and slept better. The three patients who received all seven courses stated that the necessity for trips to the emergency room or office for relief of attacks was markedly reduced. Much less of their usual medication was required to maintain their generally satisfactory condition.

Of particular interest is the fact that effects were prolonged for many months after the cessation of medication. A few patients, who received medication for twelve to sixteen weeks, were controlled through the winter months and well into the warmer weather.

Cultures of bacterial pathogens showed the same significant differences between the four groups. Organisms usually remained virulent in patients treated only with buccal protease. Those on antibiotics alone had some decrease in *Diplococcus pneumoniae,* but very little in *Staphylococcus aureus.* In contrast, *Hemophilus influenzae* and *Diplococcus pneumoniae* colonies were eliminated in those patients of group C who had three or more courses of treatment. There was also a significant decrease in *Staphylococcus aureus.* No changes in bacterial population counts were noted in patients in the placebo group.

DISCUSSION

Evaluation of results perforce were based on subjective improvement in the criteria previously cited rather than upon respiratory function tests. These tests, including maximal breathing capacity, vital capacity, and residual trapped air, were done for all patients. The maximal breathing capacity was found to be 60 per cent of "normal" in the chronic asthmatic patient before therapy. However, there were few significant changes in patients of any of the four groups during and after therapy. This also was true of the other tests, extending even to respiratory and expiratory baseline determinations. Removing, or significantly decreasing the infection

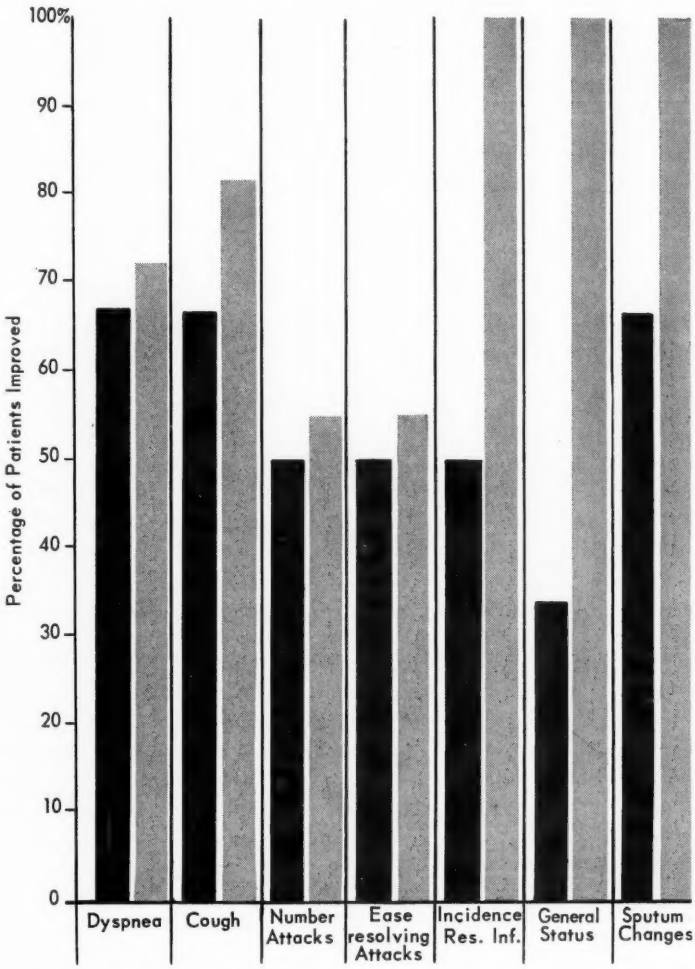

Fig. 1. Comparison of different courses of therapy for seventeen patients receiving combined buccal protease and antibiotics (Group C). Greatest improvement was observed in patients receiving courses of both buccal protease and antibiotics (Group C). Within this group degree of response was correlated with number of courses administered to patients. Solid blocks indicate less than three courses of therapy. Dotted blocks indicate more than three courses of therapy.

would not be made manifest through respiratory function tests. Since clinical results among the four groups clearly indicate the significant improvement in patients receiving buccal protease and antibiotics, it would seem that more selective and revealing types of function tests are sorely needed.

SUMMARY AND CONCLUSIONS

1. Buccal protease allows specific antibiotic agents to reach previously walled off areas of infection and inflammation.

2. The combination of buccal protease and antibiotic agents offers an excellent weapon for treatment of the patient with chronic bronchial asthma of infectious (intrinsic) nature.

3. Either of these agents used alone is not as effective as the combination of the two forms of therapy.

4. Prolonged treatment with buccal protease and antibiotic agents markedly alleviates the chronic smoldering infection so distressing to these patients.

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111 North Wabash Avenue (Dr. Frankel)

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STUDIES IN ANAPHYLAXIS

V. Desensitization: Its Theoretical and Practical Significance

RICHARD WEIL, M.D.

THE EXPERIMENTS included in the present paper aim at a study of desensitization, or antianaphylaxis, by means of quantitative methods. In a previous paper it was shown that hypersensitiveness, or the anaphylactic condition, varies in intensity, depending upon the amount of the sensitizing dose. It seemed, therefore, not unlikely that the process of desensitization might be subject to variations of a similar kind. The practical application of this problem lies in the fact that desensitization has been widely recommended by Besredka and others in connection with the administration of therapeutic sera with the object of avoiding anaphylactic shock in human beings.

The problem has been approached by the methods both of active and of passive sensitization. In order to make a quantitative study of desensitization after active sensitization, two series of guinea-pigs were selected of approximately the same weight, ranging from two hundred to two hundred and fifty grams. One series was sensitized by the subcutaneous administration of .01 cubic centimeter of horse serum. The other series received two cubic centimeters, given three times on successive days, also subcutaneously. In both series several data were determined, namely: (1) the earliest appearance of the hypersensitive condition (the so-called incubation period), (2) the minimal anaphylactic (or lethal) dose (m.a.d.), (3) the minimal desensitizing dose (m.d.d.), and (4) finally the approximate content in immune bodies of the serum. These data are summarized in the following tables. An injection of the antigen which follows immediately on sensitization, i.e., without the intervention of a desensitizing injection, is described in the tables as a primary anaphylactic injection. An injection of the antigen which has been preceded by a densensitizing dose is described as a secondary anaphylactic injection. The object of the former is to determine quantitatively the degree of hypersensitiveness; of the latter, the effectiveness of desensitization.

The first four animals were devoted to a determination of the incubation period. It is seen that after fourteen days the anaphylactic condition is not fully developed, whereas after sixteen days typical death supervenes. This

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TABLE I.

All of the guinea-pigs included in the following table were actively sensitized towards horse serum by means of a subcutaneous injection of one-hundredth (0.01) of a cubic centimeter. The guinea-pigs weighed from 200 to 250 grams.

G.P.	Primary Anaphylactic Injection	Desensitizing Injection	Secondary Anaphylactic Injection	Result
1	14th day, 0.1 cc. H.S., i.v.			Mild symptoms
2	14th day, 0.5 cc. H.S., i.v.			Mild symptoms
3	16th day, 0.3 cc. H.S., i.v.			*
4	18th day, 0.1 cc. H.S., i.v.			*
5	19th day, 0.01 cc. H.S., i.v.			Mild symptoms
6	19th day, 0.02 cc. H.S., i.v.			Convulsions; recovered
7	19th day, 0.05 cc. H.S., i.v.			*
8	19th day, 0.05 cc. H.S., i.v.			*
9		20th day, 0.001 cc. H.S., i.p.	21st day, 0.5 cc. H.S., i.v.	*
10		20th day, 0.005 cc. H.S., i.p.	21st day, 0.5 cc. H.S., i.v.	*
11		20th day, 0.005 cc. H.S., i.p.	21st day, 0.5 cc. H.S., i.v.	*
12		20th day, 0.008 cc. H.S., i.p.	21st day, 0.5 cc. H.S., i.v.	Severe symptoms
13		20th day, 0.01 cc. H.S., i.p.	21st day, 0.5 cc. H.S., i.v.	Moderate symptoms
14		20th day, 0.01 cc. H.S., i.p.	21st day, 0.5 cc. H.S., i.v.	Mild symptoms
15		20th day, 0.01 cc. H.S., i.p.	21st day, 0.5 cc. H.S., i.v.	Mild symptoms

The abbreviations employed in this and in subsequent tables, have the following meanings: H.S., horse serum; s.c., subcutaneously; i.p., intraperitoneally; i.v., intravenously; * denotes immediate anaphylactic death. The sensitizing dose was given subcutaneously; the desensitizing dose intraperitoneally; and the anaphylactic injection, whether primary or secondary, intravenously.

period is usual in the course of my experience, although other observers have determined a much shorter incubation period. The minimal anaphylactic dose, as determined in Animals 5, 6, 7, and 8, is found to lie between .02 and .05 cubic centimeter. The minimal desensitizing dose is .008 cubic centimeter, although this dose was not large enough to avert threatening symptoms; .01 cubic centimeter may be regarded as the constant minimal desensitizing dose.

Five guinea-pigs of this series were exsanguinated, and the total plasma injected intraperitoneally into five normal guinea-pigs. Of these five two died in typical anaphylactic shock upon the intravenous injection of horse serum, while three survived after manifesting moderate symptoms.

In (*sic*) second set of guinea-pigs, described in Table II, the same data were determined for a series in which sensitization had been induced by repeated large injections.

An analysis of this table reveals the following facts: The anaphylactic state is developed within ten days of the final injection. The minimal primary anaphylactic dose is .4 of a cubic centimeter. The constant minimal desensitizing dose is greater than .2 cubic centimeter of horse serum, even when this amount is given intravenously.

TABLE II.

All of the guinea-pigs of this series were actively sensitized by means of the subcutaneous administration, on three successive days, of two (2) cubic centimeters of horse serum. The weights were approximately the same as in the preceding table. The days are reckoned from the third injection.

G.P.	Primary Anaphylactic Injection	Desensitizing Injection	Secondary Anaphylactic Injection	Result
1	10th day, 0.2 cc. H.S., i.v.			Mild symptoms
2	10th day, 0.2 cc. H.S., i.v.			Mild symptoms
3	10th day, 0.4 cc. H.S., i.v.			* 8 minutes
4	10th day, 0.5 cc. H.S., i.v.			* 4 minutes
5		10th day, 0.03 cc. H.S., i.p.	11th day, 0.8 cc. H.S., i.v.	* 2 minutes
6		10th day, 0.05 cc. H.S., i.p.	11th day, 0.7 cc. H.S., i.v.	Convulsions; * 2 hours
7		10th day, 0.05 cc. H.S., i.p.	11th day, 0.8 cc. H.S., i.v.	* 15 minutes
8		10th day, 0.1 cc. H.S., i.p.	11th day, 0.7 cc. H.S., i.v.	* 10 minutes
9		10th day, 0.2 cc. H.S., i.v.	11th day, 0.7 cc. H.S., i.v.	Severe symptoms
10		10th day, 0.2 cc. H.S., i.v.	11th day, 1.0 cc. H.S., i.v.	* 2 minutes

Three guinea-pigs of this series were exsanguinated on the tenth day, and fractional amounts of their plasma injected into normal guinea-pigs. It was found that one-third of the total plasma from one pig, and one-half of that from the other two, suffice to produce passive sensitization.

A comparison of Tables I and II confirms the conclusions drawn in a previous study, namely, that a small sensitizing dose is followed by a relatively prolonged incubation period; that the minimal anaphylactic or lethal dose is small; and that the blood contains as a rule not more than one sensitizing unit. On the contrary, after repeated, large sensitizing doses, the incubation period is short; the minimal lethal dose is large; and the blood contains several sensitizing units. To these data may now be added a further observation. After a small sensitizing dose the minimal desensitizing dose is small; in Table I it is found to be .01 cubic centimeter. After a large sensitizing dose the minimal desensitizing dose is large; in Table II it exceeds 0.2 cubic centimeter. Thus, the m.d.d. of Series II is more than twenty times as great as in Series I. In fact, the minimal desensitizing dose in Table II, even when given by vein, is four times as great as the minimal lethal dose in Table I. These relative values are summarized in Table III.

TABLE III.

Sens. Dose	Inc. Period	Min. Anap. Dose	Min. Desens. Dose	Circulating Sens. Units
0.01 cc.	16 days	0.02 to 0.5 cc.	0.01 cc.	One or less
2 cc. x 3	10 days	0.4 cc.	0.2 cc.	Two or more

It seemed probable that the difference determined in the desensitizing doses might depend upon the difference in the amounts of immune bodies present in the two series of animals. In order to determine this question,

TABLE IV.

The guinea-pigs in this series received intraperitoneally a dose of two-tenths (0.2) of a cubic centimeter of rabbit serum 504, highly immunized against horse serum.

G.P.	Primary Anaphylactic Injection	Desensitizing Injection	Secondary Anaphylactic Injection	Result
1	3d day, 0.01 cc. H.S., i.v.			*
2	3d day, 0.008 cc. H.S., i.v.			*
3	3d day, 0.005 cc. H.S., i.v.			*
4	3d day, 0.003 cc. H.S., i.v.			Severe symptoms
5		2d day, 0.001 cc. H.S., i.p.	3d day, 0.01 cc. H.S., i.v.	*
6		2d day, 0.005 cc. H.S., i.p.	3d day, 0.4 cc. H.S., i.v.	*
7		2d day, 0.006 cc. H.S., i.p.	3d day, 0.4 cc. H.S., i.v.	Mild symptoms
8		2d day, 0.01 cc. H.S., i.p.	3d day, 0.3 cc. H.S., i.v.	No symptoms
9		2d day, 0.01 cc. H.S., i.p.	3d day, 0.3 cc. H.S., i.v.	No symptoms

The serum of rabbit, 504, tested on controls, the same day, sensitized guinea-pigs in amounts of 0.1 cubic centimeter.

resort was had to the method of passive sensitization. Blood was drawn from a rabbit which had been immunized against horse serum by means of repeated intravenous injections. One series of guinea-pigs was passively sensitized by means of the injection of a relatively small amount of this serum, whereas a second series was sensitized by means of a much larger amount. These two series differed, then, only in the amounts of immune, or anaphylactic, antibody which the guinea-pig possessed. In each series the minimal desensitizing dose was then determined. An experiment similar to this was performed by Doerr and Russ, with the exception that the two series of guinea-pigs used for comparison were sensitized, respectively, with serum derived from two different rabbits, instead of with different amounts of serum derived from the same rabbit.

The primary anaphylactic dose of horse serum after sensitization by .2 cubic centimeter of 504, is found to be .005 cubic centimeter. The minimal densensitizing (*sic*) dose determined was .006 cubic centimeter.

After sensitization by 1.5 cubic centimeters of 504, the primary anaphylactic dose is again found to be .005 cubic centimeter of horse serum. The minimal desensitizing dose exceeds .02 cubic centimeter, but is less than .04 cubic centimeter.

A comparison of Tables IV and V reveals the fact that the minimal lethal dose of horse serum is, in each case, close to .005 cubic centimeter. The minimal desensitizing dose, however, is more than three times as great, and probably at least four times as great, after passively sensitizing with large amounts (1.5 cubic centimeter) of immune rabbit serum, as it is when small amounts (.2 cubic centimeter) are used. Moreover, the minimal desensitizing dose of Table V is at least four times as great as the m.a.d. of Table IV, although it must be remembered that the former is

TABLE V.

The guinea-pigs of this series received, intraperitoneally, one and one-half (1.5) cubic centimeters of Serum 504, on the same day as those of the preceding table.

G.P.	Primary Anaphylactic Injection	Desensitizing Injection	Secondary Anaphylactic Injection	Result
1	3d day, 0.01 cc. H.S., i.v.			*
2	3d day, 0.005 cc. H.S., i.v.			*
3	3d day, 0.0025 cc. H.S., i.v.			Symptoms
4		2d day, 0.006 cc. H.S., i.p.	3d day, 0.05 cc. H.S., i.v.	*
5		2d day, 0.008 cc. H.S., i.p.	3d day, 0.01 cc. H.S., i.v.	*
6		2d day, 0.01 cc. H.S., i.p.	3d day, 0.1 cc. H.S., i.v.	*
7		2d day, 0.02 cc. H.S., i.p.	3d day, 0.1 cc. H.S., i.v.	*
8		2d day, 0.04 cc. H.S., i.p.	3d day, 0.1 cc. H.S., i.v.	Mild symptoms

administered intraperitoneally, the latter intravenously. These comparative data are summarized in Table VI.

It is, therefore, evident that the presence of a large number of specific antibodies in a guinea-pig requires the use of a larger amount of the antigen in order to produce desensitization. The exact ratio between these two factors, if there be such a ratio, has not been determined. Where the number of sensitizing units was seven and a half times as great, the minimal desensitizing dose (m.d.d.) was found to be more than three times as large. Aside from the exact quantitative relationships, however, it seems permissible to conclude from these results obtained in passive sensitization that the m.d.d. in guinea-pigs which have been actively sensitized is determined by the method of sensitization. Where a single fractional dose has been employed to sensitize, the resulting antibody production is not great, relatively speaking, and the m.d.d. is correspondingly low. On the contrary, where several large doses of antigen have been injected, the antibody reaction is powerful, and the m.d.d. is high.

TABLE VI.

Sensitizing Dose	Primary Anaphylactic Dose	Desensitizing Dose
0.2 cc.	0.005	0.006
1.5 cc.	0.005	0.02-0.04

These data have a certain importance from the standpoint of human disease. It is, of course, a well known fact that the subcutaneous administration of diphtheria antitoxin may be the cause of more or less severe symptoms. These results may follow upon either a first or a later injection, and have almost universally been considered as manifestations of anaphylaxis. Recent studies by Nemmser[1] and Goodall[6] demonstrate however, that

subcutaneous inoculations of serum, even in cases in which there has been a previous use of the same serum may, indeed, be associated with more or less striking symptoms, but that death is an extremely rare result. These phenomena in human disease are in accord with the results of animal experimentation, which demonstrate that even highly sensitized animals can tolerate relatively large doses of serum when given by the subcutaneous route; marked symptoms may occur, but rarely death.

There has, however, been a strong tendency of recent years to substitute the intravenous administration of therapeutic sera for the subcutaneous route. This has been recommended not only in the case of diphtheria, but also of tetanus antitoxin. The reasons for this procedure are, indeed, cogent, and have recently been carefully analyzed by Park,[12] who reports its use in two hundred cases without a serious accident. On the analogy of animal experimentation there can be no doubt that this mode of administration, however, is fraught with considerably greater danger to the patient from the standpoint of serum anaphylaxis. For the mild symptoms which ensue on the subcutaneous administration, severe symptoms would certainly be substituted in intravenous administration; and instead of severe symptoms there might be death.

But it is not only the intravenous mode of serum administration which, indeed, has not as yet come into general use,—that is associated with greater danger than the older methods. The introduction of intraspinous serum therapy in connection with epidemic meningitis also materially increases the risk of anaphylactic symptoms as compared with the subcutaneous route. This is due not only to the fact that absorption is very much more rapid in the spinal canal than in the subcutaneous tissues, but also to the fact that a concomitant inflammatory condition materially hastens the rate of absorption (Friedberger and Lurà[5]). This fact was emphasized some time ago by Besredka,[2] who pointed out that the intraspinous use of anti-meningococcus serum had suddenly brought into unpleasant prominence the question of "serum disease," which had previously, in connection with the subcutaneous use of anti-diphtheritic serum, scarcely attracted serious notice. He mentions ten fatal cases in Paris alone, resulting from this mode of therapy, and quotes the fact that Hutinel[8] had observed four such calamities.

In order to obviate such occurrences, Besredka suggested the application in human beings of the method of desensitization which had been studied by him with great elaboration in animals. In a series of experiments on guinea-pigs he found that the sensitized animal could be efficiently protected against the fatal dose of serum given intraspinally, if the animal had previously received a properly graded dose of serum either under the skin, into the peritoneum, intraspinally, or intravenously. As to the results obtained by Besredka in his animal experiments there can, indeed, be no question. There is, however, a serious difficulty in applying these results directly to the treatment of human beings. In the animal experiments it

was known that the guinea-pigs had been sensitized by a certain dose of antigen, and it was known of the entire series that a certain definite amount of serum was necessary, to produce death. Hence, it was a simple matter to determine, approximately, the dose necessary to desensitize these animals and to preserve them from a fatal outcome on the final injection. Unfortunately, these data are not known in human disease. There are, in the first place, a considerable number of individuals, for example, asthmatics, who seem to be constitutionally predisposed to serious symptoms, or even death, upon the injection of small amounts of horse serum, even though they have never received a preceding injection. In the second place there are the other individuals, of various sizes and weights, who have received one or more doses of therapeutic horse serum in various amounts at varying intervals before the administration of a contemplated injection. In such cases it is extremely difficult—if not absolutely impossible—to calculate the probable fatal dose of serum in intraspinous or intravenous injection. It follows that the proper dose to secure desensitization is, in such cases, highly problematical. The data adduced in the first part of this paper indicate that a minimal desensitizing dose for one group of individuals might amount to four times the fatal dose for another group. The difficulties of the situation are not exaggerated by the procedures employed in the animal series, summarized in Tables I and II of this paper. It is customary, in spinal meningitis, to give repeated and large doses of the serum in order to control the disease, while single small doses often suffice in cases of diphtheria. It is, therefore, reasonable to conclude that human beings who have received these various modes of treatment, would differ from each other no less strikingly than do the animals of Tables I and II. As a matter of fact there is clinical evidence that these conditions do actually obtain, and that the preliminary use of a desensitizing injection may entirely fail of the expected effect.

This difficulty was not thoroughly appreciated by Besredka. In all of his experiments in active sensitization he made use of fractional sensitizing doses. Indeed, in his review of anaphylaxis, in Kraus and Levaditi's[3] handbook, he explicitly states that the preliminary injection of amounts larger than one-fiftieth of a cubic centimeter of serum cannot be relied on to produce a sensitive condition. This conclusion was based on results obtained with the intracranial method of injection for the toxic dose. But, as has been amply shown in this and in a previous paper,[14] the intravenous method of injection demonstrates that guinea-pigs prepared by repeated massive injections of serum are hypersensitive in the same sense as those prepared by fractional doses. The important fact, which apparently escaped Besredka, is that such animals can be desensitized only by doses of serum very much in excess of those required after sensitization by minute doses.

Now, human beings react in this respect exactly as do the guinea-pigs. The four fatal human cases reported by Hutinel illustrate this fact. In each of them the patient had received several large intraspinal injections of

serum; after an interval of a varying number of days, in each of them, another intraspinal injection was given, which resulted in a violent explosion of symptoms and death. Hutinel rightly attributes this series of disasters to an actively induced anaphylaxis. Netter[11] refers to two more similar cases, although it is not clear whether or not death occurred.

On the analogy of the guinea-pig experiments, it would be expected that such patients could not be desensitized except by the intermediate injection of very large doses of serum. And such, indeed, proves to be the fact.

Thus, a case very much in point has recently been recorded by Grysez and Dupuich.[7]

In this instance, anti-meningococcus serum had been given in considerable quantities and a number of times, with arrest of the symptoms. Three weeks after the injections were discontinued the symptoms returned. Another intraspinous injection was planned. In order to avert shock, the authors gave a preliminary intraspinous dose of two cubic centimeters of serum. Nevertheless, the subsequent intraspinous injection was associated with most critical symptoms of anaphylactic character, which seem to have threatened the death of the patient.

Besredka[1] has recently suggested that desensitization might be rendered still more certain by the use of repeated, instead of single, preliminary doses. These are given at fairly short intervals, and are graduated in such a way that the last dose is many times as large as the first. This is known as the method "de doses subintrantes." There can be no question that this method is extremely effective, but it also holds true, as of the single preliminary dose, that in order to be intelligently applied, it must be based upon some knowledge of the degree of sensitization present. The following table illustrates both the weakness and the strength of the method.

TABLE VII.

The animals of this series were sensitized with the same serum in the same amount as those of Table VI., namely, 1.5 cubic centimeters of S. 504. The fatal primary anaphylactic dose, as ascertained in Table VI., is 0.005 cubic centimeter of horse serum.

G.P.	First Desensitizing Injection	Second Desensitizing Injection	Anaphylactic Injection	Result
1	2d day, 0.001 cc. H.S., i.p.	2d day, 1 hour later 0.005 cc. H.S., i.p.	3d day, 0.05 cc. H.S., i.v.	*
2	2d day, 0.001 cc. H.S., i.p.	2d day, 1 hour later, 0.005 cc. H.S., i.p.	3d day, 0.05 cc. H.S., i.v.	*
3	2d day, 0.01 cc. H.S., i.p.	3d day, 0.005 cc. H.S., i.v. *Convulsions*	3d day, after 15 min., 0.2 cc. H.S., i.v.	*
4	2d day, 0.01 cc. H.S., i.p.	3d day, 0.01 cc. H.S., i.v. *Severe symptoms*	3d day, after 1 hour, 0.2 cc. H.S., i.v.	*

There are a number of important facts brought out by this table. In the first place, it is clear that a repetition of preliminary doses does not necessarily induce desensitization. In the second place it will be observed that two animals (Nos. 3 and 4) of this series received intravenously as a second dose an amount of horse serum which had proved fatal in the

controls. Hence, one may conclude that the intermediate administration of serum had rendered these animals somewhat refractory, so that an ordinarily fatal dose failed to kill. This is an observation which I have frequently made; a somewhat larger dose, such as .1 or .2 cubic centimeter would, however, undoubtedly have produced anaphylactic death. In the third place, both of these animals had very severe symptoms, which in one took the form of convulsions. Notwithstanding this, a somewhat larger injection shortly thereafter resulted in death. This is an observation on which stress has been laid by other observers. Doerr[4] states that he has repeatedly seen exactly this succession of events, namely, that a guinea-pig sensitized either actively or passively may respond with symptoms of very severe shock to an injection of antigen, on one day, and be killed by the same antigen on the day following. Moreover, Netter[11] observed the identical phenomenon in a "desensitized" human patient.

It seems safe to conclude, therefore, that the use of "doses subintrantes" does not afford a reliable guarantee of safety in human therapeutics any more than does the single intermediate dose. Even in cases in which an intermediate series of doses has included an ordinarily fatal dose, or in which the individual under treatment has manifested very severe symptoms, and has recovered therefrom, there is no certainty that a somewhat larger dose, given after a short interval, will not produce death. In animal experimentation it is always possible to save a sensitized guinea-pig by means of a properly graduated series of "doses subintrantes," provided one knows the mode of sensitization and the minimal anaphylactic dose. Without this knowledge the method loses materially in certainty, and is bound in a large proportion of instances to meet with failure. Under the conditions which exist in the treatment of disease, this uncertainty is the factor which robs the method of the reliability which has been claimed for it.

Lissowskaja[9] (cit. by Doerr) and Rosanow[13] (cit. by Doerr) have stated that human beings may be protected against the possible serious results of an intravenous injection of therapeutic serum by means of an intermediate intramuscular or subcutaneous injection of the serum, using .05 cubic centimeter per kilo of body weight. Rosenow, indeed, has gone further and has advocated the preliminary injection of a desensitizing dose of from .4 cubic centimeter to two cubic centimeters, intravenously. These recommendations, as Doerr points out, are placed upon a very questionable footing by the actual clinical experiences of Netter, and of Grysez and Dupuich. It is hardly necessary, in view of the experiments described in this paper, to point out that it would be dangerous in the extreme to place any reliance upon routine measures of this sort.

In his review of anaphylaxis Besredka[3] states that we may confidently look forward to the time when our whole method of serotherapy will have become changed by the substitution of the intravenous for the subcutaneous route. "And although," says he, "clinicians have hitherto rightly feared to introduce therapeutic sera directly into the blood stream, this hesitation

may now be considered as terminated by the discovery of a positive and reliable method of avoiding the symptoms which might result therefrom." It would seem at the best uncertain. Only a special indication would seem to justify the risk associated with an intravenous administration in cases where previous injections have been made. As regards the use of intraspinous injections, especially where an interval of a few days has passed since the preceding application of serum, it should always be borne in mind that there is serious danger of anaphylactic symptoms. Such individuals are highly sensitized, as has been shown by the cases recorded by Hutinel, Netter, and others. In view of the fact that it is customary in meningitis to introduce large doses of serum, often on successive days, such cases may properly be compared with the guinea-pigs of Table II (*sic*) in this paper, in which sensitization has been induced by the administration of three successive doses of two cubic centimeters of horse serum. In such individuals the use of a prophylactic desensitizing dose would afford slight hope of averting anaphylactic shock unless, indeed, relatively enormous amounts were used. The case of Grysez and Dupuich[7] is an illustration of this fact. It may properly be said, therefore, that if desensitization is attempted in such cases, relatively enormous doses of horse serum must be injected subcutaneously.

Whether the cases of serum sickness following upon a first injection of anti-meningitis serum intraspinally are to be attributed to a constitutional sensitization towards horse serum remains an open question. This explanation has been accepted of the rare cases of death consequent upon a first injection of diphtheria antitoxin subcutaneously. If such is the case, undoubtedly the danger of anaphylactic shock or death would be very much increased by the intraspinous method of administration. Not only the greater amounts but the increased rapidity of absorption would tend to produce death in many individuals who would simply manifest moderate symptoms upon the injection of an ordinary dose of diphtheria antitoxin subcutaneously. Seven cases with severe symptoms were reported by no less an authority than Netter.[11] It is probable that a certain proportion could be saved by the preliminary injection, by the subcutaneous route, of large doses of horse serum. There is no certainty as maintained by Besredka, that such treatment will effectively protect every patient, but there is reason to hope that it would save some of them. As opposed to this recommendation is the possible disadvantage of introducing large quantities of serum into the body of a patient who will have to dispose of additional amounts when the local therapeutic injections are made into the spinal canal. Whether the latter consideration is ever sufficient to contraindicate the use of the method must be determined by future experience.

CONCLUSIONS

1. The conclusion drawn in a previous paper is verified, namely, that the mode of sensitization determines certain important factors in active

anaphylaxis. Guinea-pigs sensitized by the injection of fractional amounts of alien serum present a prolonged incubation period, require a relatively small dose of antigen to produce death, and contain in their serum relatively few specific antibodies. On the contrary, guinea-pigs sensitized by repeated large injections of alien serum present an abbreviated incubation period, require a much larger dose of antigen to produce death, and have many more antibodies in their serum.

2. To these data is added the fact that after active sensitization by fractional amounts of alien serum, the minimal desensitizing dose is relatively very small. After sensitization by repeated large doses, the minimal desensitizing dose is many times as large as in the previous case, and may even very largely exceed the minimal lethal dose there determined.

3. After the passive sensitization of guinea-pigs by small and by large amounts of immune rabbit serum, respectively, it is found that the minimal desensitizing doses are small, and large, respectively. Hence, the deduction is drawn that in active anaphylaxis, also, the amount of the minimal desensitizing dose is determined by the relative number of specific antibodies possessed by the animals.

4. Repeated desensitizing injections ("doses subintrantes") are subject to the same conditions as control the effectiveness of the single dose. Moreover, it is shown that recovery from severe anaphylactic symptoms, or from the administration of a dose fatal for control animals, does not necessarily avert a fatal result upon the administration of a larger dose on the succeeding day.

5. Cases are cited to show that human beings are sensitized, in the same way as are guinea-pigs, by the repeated injection of large amounts of therapeutic serum, given intraspinally, and may be killed by a subsequent injection. The desensitization of these individuals offers a complex problem, which is discussed in detail. Protection against the toxic effects of primary injections presents a problem of the same character, but practically much less difficult of solution.

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Progress in Allergy

MICROBIAL ALLERGY

A Critical Review—1950-May 1960

HERMANN BLATT, M.D., F.A.C.A.
Cincinnati, Ohio

PART II

(Continued)

MICROBIAL ALLERGY OF THE EYE

Conjunctivitis is one of the most common forms of ocular allergy. Almost any allergen can be the offender although a toxin-producing staphylococcus is the most frequent bacterial cause of allergic conjunctivitis. Woods[195] feels that such etiology should be suspected in the presence of a chronic nonpurulent conjunctivitis often associated either with folliculosis, marginal blepharitis, or reddened swollen margins of the lids. Frequently there are slight secondary corneal changes, and the toxin-producing staphylococcus can sometimes be isolated from the conjunctiva. Woods determines cutaneous sensitivity by an intracutaneous injection of 0.1 cc of a 1:100 dilution of toxin, later by an injection of 1:1000 or 1:10 dilution, depending on whether the first injection gives a positive or negative result. Normal patients react to the 1:100 dilution with an area of erythema approximately 3 to 4 cm in diameter. Greater reactions, or reactions to a weaker dilution, are signs of abnormal hypersensitivity. He desensitizes with a dilution of staphylococcus toxins, generally of a 1:100 dilution, gauged according to the degree of cutaneous sensitivity. Injections are given intracutaneously, starting with 0.1 cc at four-day intervals and continuing until the patient tolerates 0.1 cc of pure toxin. Focal inflammatory reactions may occur several hours after an injection and may last up to thirty-six hours. Hypersensitivity to streptococci and their toxins may also cause allergic conjunctivitis. Woods feels that "since there is no streptococcus toxin or vaccine which gives blanket protection, the only practical method of attacking the problem is the preparation of a killed suspension and of filtrates of cultures of the organism isolated from the patient, and testing the patient and controls against such antigens."

Acute dermatoconjunctivitis may be either of the immediate or of the delayed type, and is characterized as a dry or weeping eczema of the lids and a papillary hypertrophy of the conjunctiva. Ordinarily, the conjunctivitis is very severe and corneal changes may be present. There is a watery mucopurulent discharge from the conjunctival sac which produces an excoriation of the skin at the lateral and median canthus. Most allergic cases are caused by cosmetics, especially cream-based shampoos. Braley emphasizes that "allergy, both that of a bacterial nature and that due to contact with the staphylococcus and its products, plays an important role in the clinical picture of this disease." He further points out that not

only has *Staphylococcus albus* been used to produce the Shwartzman's phenomenon, but also that the exotoxin has a direct effect which is often antigenic.

Chronic conjunctivitis may also be of the immediate or of the delayed type, with the latter caused by an allergic response to bacteria, fungi, and possibly viruses.[188] A focal reaction occurring in the conjunctiva and usually developing immediately or within hours can take place following the intramuscular injection of penicillin. "Many of these focal reactions are similar to the Shwartzman phenomenon."

Vernal catarrh is a relatively rare disease, with the global incidence supposed to be less than 1 per cent of all eye diseases. The etiology of vernal catarrh is still unknown, but it is generally believed to be a form of allergy. Waldbott[196,197] claims that the disease is chiefly a combination of sensitivity to fungi and tree pollen, while Hansel[136] believes that it is a form of contact allergy. Theodore,[189] on the other hand, holds that the etiology may be endocrinic, metabolic, allergic, and possibly infectious with the warm season acting as a trigger mechanism to release a chain reaction that produces the clinical symptoms. Of the other observers who have studied vernal catarrh, Feinberg[198] puts the blame on fungi spores as the principal offenders, while Braley is of the opinion that it is not a typical allergic disease. Cooke,[199] on the contrary, believes many cases of vernal catarrh to be bacterial allergies and advises elimination of all foci of infection along with vaccine therapy. In my own limited experience, I have never been able to find a positive reaction to the Blatt-Nantz test in a case of vernal conjunctivitis.

Many corneal diseases are delayed type responses to microbial products, with the cultures of central corneal ulcers usually showing bacterial growth, although cultures from marginal ulcers and infiltrates are generally sterile. Theodore[200] reports that many of these cases are apparently of toxic origin, secondary to toxigenic staphylococcal infections of the conjunctiva and lid margins. Although the etiology can be endogenous bacterial allergy, the dominant mechanism often is a definite exogenous allergy to the toxin and other bacterial products.

The clinical picture of corneal allergies is a very complex one, and Braley classifies them into three basic types, as noted previously. Recently, he has observed several cases of sudden edema of the cornea associated with an allergic rhinitis. One patient, in whom the specific allergen could not be elicited, had an asthmatic attack with a severe allergic conjunctivitis. Deep vascularization followed repeated attacks, and Braley classified this clinical picture as an "acute allergic keratitis." Cases exhibiting the delayed form of corneal edema, which is associated mostly with vascularization and infiltration of the cornea, may be either contact or bacterial keratitis. Chronic keratitis may be due either to an atopic or a bacterial hypersensitivity.

According to Braley, phlyctenular keratoconjunctivitis is the most typical bacterial allergic keratitis, while Theodore and Schlossman believe that it "has always been one of the most important diseases in ophthalmology."[200] It is generally agreed that this disease is an endogenous microbial allergy, with the tuberculoprotein as the most important allergen. And as the incidence of hypersensitivity to tuberculoprotein decreases, more attention is being focused on other bacterial products, especially staphylococci, as an etiologic factor in the disease. Theodore, in his recent book "Ocular Allergy,"[200] presents an excellent review of recent studies of cases where tuberculosis was ruled out as the etiology. He reports having a patient

with phlyctenular keratoconjunctivitis who had been paralyzed many years previously by poliomyelitis and whose tuberculin test was negative. More and more cases are being reported in which the *Staphylococcus aureus* seems to be the etiologic agent. Theodore's experience is the same as Thygeson's, namely that "patients with staphylococcal phlyctenulosis have a much greater sensitivity to toxoid than do patients with other infections due to staphylococci, such as blepharoconjunctivitis."

Occasionally, phlyctenular keratoconjunctivitis is due to streptococcal products. In a small series of cases, Hanser[201] reports best results by treating with local antiseptics and Antigen-H or staphylo-toxoid. In studying thirty-seven cases of this disease from the San Francisco Bay area over a four-year period, Thygeson[202] found five cases due to sensitivity to staphylococcal proteins. These patients had certain common characteristics, the most important of which was a marked skin sensitivity to staphylococcus toxoid. Moreover, all gave positive cultures of hemolytic *Staphylococcus aureus* from the conjunctiva and eyelids. Every patient had an associated blepharitis, relapses occurred only when the staphylococci lid infection recurred, and all responded to topical anti-staphylococcus therapy. One case was due to *Candida albicans (monilia)* which developed a few weeks after the onset of a cutaneous dermatitis. Here, recurrences of the eye disease accompanied flare-ups of a skin condition. Another case was due to *lymphogranuloma venereum* virus, while there were two cases among children caused by *Coccidioides imminitis.*

The luetic form of interstitial keratitis is believed to be a delayed allergic response to spirochetal products. Both eyes are usually affected; when only one is involved, the second eye sooner or later becomes affected also. The explanation of this condition, which is generally a late symptom of hereditary lues (rarely of acquired syphilis) remains unsolved. Tassman[203] suggests that interstitial keratitis may be a sensitization of the cornea caused by an early infection and resulting in allergy to the products of the system. The disease presents several varieties, in one of which opacification starts in the center of the cornea in the form of maculae. In other varieties, it starts peripherally and gradually infringes upon the center. A characteristic feature is various degrees of vascularization. A little gives the cornea the appearance of "ground glass" and more gives the cornea a uniform reddish appearance which resembles "salmon patches." The tuberculous variety of interstitial keratitis is similarly believed to involve the mechanism of a delayed response.[192] In tuberculous interstitial keratitis, ordinarily only one eye is involved, and frequently the condition is confined to only one portion of the cornea, which shows a marked nodular infiltration. The vascularization is present in the middle and deep layers.

Disciform keratitis is believed to be a delayed type of allergic reaction due to the herpes simplex virus.[192] Usually only one eye is involved, and a number of disc-shaped opacities are found under the Bowman's membrane, which are, for the most part, centrally located. In later stages, the discs become sharply outlined and depressed in the center with the formation of a facet which gives a characteristic appearance.

In an article on the clinical features of viral keratitis and its pathogenesis, Jones[204] labeled the corneal stroma as an "immunological blotter." According to his theory, the viruses, after growing in the epithelial cells, liberate antigens which soak into the underlying stroma and become fixed in the surface of the fiber and cell membranes. Antibodies, either from the blood stream or of local origin, effect an altered permeability and stromal edema by reacting with the herpetic antigen on the surface of the corneal lamellae.

This not only produces opacity, but intense reactions cause necrosis as well.

In his comprehensive annual review on the cornea and sclera, Thomas[205] cites an interesting case of ophthalmomycosis. After sensitization by plantar interdigital dermatophytosis, an association was observed of a dyshidrosis-like rash, especially of the hands, and vesicles with a sterile content on the limbus. Thomas states that "in the pathomechanism of localization in allergic ophthalmodermoses, it is assumed that trauma suffered previously by the sensitized organ as well as its blood supply have an influence. The slowed blood flow in the vascular anastomoses of the limbus was thought to promote invasion of the adjacent tissues by the allergens."

Braley[188] considers herpex simplex keratitis to be a hypersensitive phase of the reaction to the virus, as the disciform keratitis following herpes infection is, in his opinion, a manifestation of hypersensitivity. A high titer of neutralizing antibodies and complement-fixing substances can be found circulating in the blood, but although complement-fixing substances probably are a factor in immunity, Braley believes that the neutralizing antibodies play "little or no role in preventing infection." Because the response to the herpes infection is mainly one of edema, these antibodies may represent a local manifestation of the allergic state, which would be responsible for the corneal reaction. Braley could not prove this completely, but he reports that some serum herpes mixtures, when injected into mice, caused immediate anaphylactic death.

Theodore and Schlossman[192] are of the opinion that there are two types of disciform keratitis: (1) a form without clinical evidence of herpetic keratitis, and (2) the type occurring in association with demonstrable herpetic ulceration. The first variety may possibly be allergic in nature. In the second form, where a herpetic ulcer pre-exists, "while allergy possibly operates in the production of the stomal edema, the infectious component of the process predominates to the extent that corticosteroids must not be used." Since the herpetic form of keratitis is more common, Theodore emphasizes the importance of a thorough history and examination before steroid therapy is instituted, in order to rule out herpetic infection.

Marginal ulcers and infiltrates play an important role in staphylococcal conjunctivitis, and based on their own observations, Theodore and Schlossman are convinced that more marginal ulcers and infiltrates occur without an associated conjunctivitis than are reported in statistics. "Perhaps such cases are due to other allergic phenomena, rather than to microbial allergic reactions in conjunctivitis." Occasionally, there are cases of margin lesions in atopic allergies such as foods. Keratoconjunctivitis due to contact allergy can sometimes be confused with marginal reactions in conjunctivitis due to bacterial allergy,[192] although conjunctival cultures and scrapings will help to differentiate the two conditions. Braley[188] believes that the marginal ulcers and infiltrates in staphylococcal conjunctivitis are reactions similar to the Arthus phenomenon.

Despite the fact that it is not conclusively proved, observers are generally agreed that most cases of marginal ulcers in bacterial conjunctivitis are of an allergic nature. Theodore and Schlossman[192] present the following arguments in favor of an allergic etiology: (1) marginal ulcers usually appear after the infection has been present for a period of time; (2) the patient frequently has positive skin tests to bacterial exotoxins or some foci of infection; (3) it is difficult to isolate bacteria from scrapings of marginal ulcers; (4) Thygeson never observed a catarrhal ulcer caused by the pneumococcus, and no exotoxin has been observed in association with

pneumococci; (5) many similarities between marginal ulcers and phlyctenules exist which are conceded to be allergic manifestations; (6) marginal ulcers have been observed in both atopic and contact allergies, as well as in vernal catarrh; (7) these ulcers generally respond well to corticosteroids.

The etiology of ring ulcers, although allergic in nature, differs from that of marginal ulcers. Although they probably are a result of systemic microbial allergy, Theodore and Schlossman did recently observe a case of bilateral severe ring ulcers with normal bacterial flora and without any evidence of infection throughout the body.

Many cases of scleritis and episcleritis are delayed reactions to streptococci or tuberculoproteins, but Theodore[192] believes that it has yet to be proven whether or not episcleritis from leprosy is a delayed reaction.

Keratoconjunctivitis associated with acne rosacea is not uncommon, and although its etiology remains unknown, some authors assume that it is due to bacterial allergy.[206,207]

At the January 1960 meeting of the British Association of Allergists, A. G. Cross[208] spoke on the "allergic manifestations of the conjunctiva and uveal tract." From his paper, one gains the impression that Cross does not believe in the existence of such a thing as microbial allergy. He states that "while some cases appear to be due to invasion of the eyeball by bacteria, the large majority appear to have an allergic cause." He argues for the frequently allergic, rather than bacterial, nature of this condition by maintaining that "the absence in all cases of any organisms in the affected eyeball, the prolonged course of the condition with final subsidence, and the astounding response to treatment with steroid therapy are very suggestive that uveitis is allergic in origin." To many investigators, these observations would confirm the possibility of allergy, without excluding the fact that some of these cases may be a form of microbial allergy. Nevertheless, most investigators today agree that allergy, especially bacterial allergy, plays a very definite role in certain forms of uveitis. Coles[209] points out that even in the granulomatous type of uveitis, where microorganisms may be demonstrated, a secondary microbial allergy often alters and aggravates the inflammatory state. In his book on endogenous uveitis, Allen C. Woods[210] states that streptococci, staphylococci, and gonococci account for approximately 80 per cent of the cases of nongranulomatous uveitis, with streptococci as the most common offending organism. Woods recommends the making of autogenous cultures and skin testing intradermally with isolated strains, because the specific microbial allergen must be determined even at the expense of surgical interference.

When the culture shows any streptococcus, colon organisms, pseudomonas or any other suspicious strains, the detected bacteria should be isolated in pure culture, a vaccine made, and the patient treated against such a vaccine. Staphylococci can generally be omitted, since they are chiefly secondary invaders, and hypersensitivity to staphylococci can be covered by a staphylococcus test. Woods finds that the work of Berens and his group[211] "has produced considerable circumstantial evidence likening the coliform bacteria to uveitis, and if such organisms are found, the question of a specific hypersensitivity to them should be investigated.

A specific vaccine, when given in a therapeutic dose that may produce a marked reaction in the eye, is dangerous. Since this is so, very weak dilutions should be tried first. A flare-up following an injection and clinical improvement following desensitization are evidence of the bacterial etiology of the disease, while a systemic rather than a local reaction speaks

against a relationship of the vaccine to the disease of the eye. In the latter case, however, it may indicate a relationship to some other disease processes in the body, or it may reveal an allergy to one of the nutriments used in culturing the bacteria or to a chemical used in a process of making the vaccine.

A single insult of bacterial antigen is the cause of non-granulomatous uveitis, which, according to Woods,[210] is self-limited. If the tissues continue to be attacked by antigen, however, the disease is prolonged and organic changes take place that may resemble advanced granulomatous uveitis. Chronic cases have an epithelial reaction resembling rheumatic nodules.

A very important publication appeared in 1958, "The Uveitis Symposium," which was published in the *Survey of Ophthalmology*. The Symposium had as participants not only ophthalmologists, but also immunologists, microbiologists, virologists, and rheumatologists. The Symposium concerned itself mainly with granulomatous uveitis. The present day concepts of hypersensitivity were reviewed.

Coles[209] is in disagreement with Woods' theory of streptococcal sensitivity as a cause of nongranulomatous uveitis. He studied the antistreptolysin O titer in anterior uveitis. Three hundred and one antistreptolysin O determinations were made on sixty patients having uveitis. Of these, 116 determinations were made on sixty patients with anterior uveitis, and eighty-nine were on thirty-two patients with posterior uveitis. A controlled series of blood was also run. Coles found no appreciable difference in any of these groups. He believes there is no casual relationship between anterior uveitis and streptococcal infection as far as can be determined from the antistreptolysin determination.

Hallett and collaborators[212] also found antistreptolysin O titer determination of little value in uveitis.

Schlaegel[213] studied 100 cases of granulomatous uveitis. Eighty-two per cent of these cases had involvement of the posterior segment; 4 per cent of the cases gave ocular flareup on skin testing with O Tuberculin; 1 per cent of the cases showed a flareup with a histoplasmin skin test. No flareups with toxoplasmins or brucellergin were noted. Toxoplasma dye tests were positive in 68 per cent of the cases compared to 58 per cent of the toxoplasma skin test positive reactions. In his annual review of the uveal tract, Kimura[214] agrees with Schlaegel's findings. Schlaegel had also used the penicillin therapeutic test, and Kimura admits that "because of the lack of a better drug we are forced to use these two." Schlaegel uses the penicillin and isoniazid test. "Since syphilis is a rare cause of uveitis today," writes Kimura, "I question the value of the penicillin therapeutic test. More, I fear that if this test becomes accepted, penicillin reactions and deaths may result."

Catterall[215] conducted an interesting study on the correlation of chronic prostatitis with uveitis in 170 patients. On 150 patients, they did stain smears of prostate gland, PPLO culture, aerobic and anaerobic organism cultures of prosthetic secretion, urine culture for PPLO, hematologic studies, and serologic tests including the complement fixation test for PPLO. Seventy-two per cent of the 150 patients with uveitis had chronic prostatitis, and 16.7 per cent of the controls who were surgical patients of the same age group; 70 per cent of the 150 patients had anterior uveitis. Catterall believes chronic prostatitis to be a common finding in patients having anterior or generalized uveitis, but that this is not true in cases of posterior uveitis. Kimura comments in his review

that this article "certainly seems to revive the hypothesis of focal infection." I agree with Coles and Theodore[216] that the theory becomes acceptable if such chronic foci are considered as antigenic foci rather than infectious.

More and more cases of iridocyclitis due to causes other than tuberculosis or syphilis are being reported in the literature, and it now is an established fact that many of these cases are caused by various microorganisms. According to Binkhorst and Van Ufford,[217] about 25 per cent uveal irritations of undetermined origin are due to toxoplasmosis, while Streiff,[218] as early as 1953, stressed focal infections as causative factors in many cases. He also pointed out that reactions of an uvea sensitized by tuberculoprotein may be due to contact with a non-specific allergen. In the excellent book "Ocular Allergy" by Theodore and Schlossman, Coles[209] emphasized, as have other investigators, that the common non-granulomatous sterile form of endogenous uveal inflammation is generally a delayed allergic reaction of the microbial type. In their recent preliminary report, Binkhorst and Van Ufford[217] gave their results in evaluating patients with iridocyclitis and uveitis, restricting themselves as to whether these patients had any evidence of an allergic constitution, and if so, what the offending allergens might be. Provocation tests were regarded as too hazardous and because the period of investigation was only of a two-year duration, no conclusions were drawn as to therapy.

The patients studied were those in whom a diagnosis of tuberculous lesions of the eyes had been made without any evidence of tuberculosis. Most of these cases had regularly high eosinophilic blood counts. Sixty-seven patients were studied, and signs of an allergic constitution were observed in a larger proportion than is usually the case. It was also noted that an injurious factor was rare in their histories, whereas a history of frequent infections was a common occurrence. With the exception of headaches and fatigue, there was no characteristic history prior to the onset of symptoms. Although remissions were frequent, more so during the spring and autumn, there was no particular exposure to allergens. The patients were intradermally skin tested with low concentrations of inhalants, foods, and bacterial antigens, the last of which included alpha, beta, and gamma streptococci, *Micrococcus pyogenes* (var. *albus* and var. *aureus*), staphylococcus toxoid, *Hemophilus influenza, Neisseria catarrhalis, Aerobacter aerogens,* Klebsiella, *Escherichia coli* and Proteus. Inhalants only occasionally gave positive reactions, while both the foods and the bacterial antigens frequently produced marked positive reactions. This was especially the case with *Micrococcus pyogenes,* streptococci, *H. influenzae,* and Gram-negative bacteria. Serologic tests, for example, anti-streptolysin titers, were carried out routinely, often with increased reactions. The sedimentation rate did not prove to be a reliable indication as to the severity of the eye manifestations. Most patients had normal blood pressure, while nineteen patients had negative tuberculin reactions. Many patients had associated inflammatory lesions, which when treated, caused at least a temporary improvement of the eye condition. One patient showed ocular reactions following staphylococcus toxoid injections. Another patient's ocular symptoms were aggravated following tonsillectomy, while one patient improved rapidly after a sinus operation.

On the basis of their studies, Binkhorst and Van Ufford are convinced that foci of infection and allergic reactions to bacteria are important factors in the pathogenesis of iridocyclitis. Since, however, such ocular reactions are observed only in a number of patients, other factors evidently are also involved.

Non-granulomatous uveitis is often associated with rheumatoid arthritis, and most investigators today believe that rheumatoid arthritis is probably an allergic reaction caused by streptococcal hypersensitivity. Hogan, Kimura, and Thygeson[219] recently published a most interesting article on this point, in which they state that we in the United States pay too little attention to the uveitis-arthritic syndromes. "The coincidence of iritis and iridocyclitis in patients with rheumatoid arthritis is of such frequency that both must be considered as secondary to the same agent." The authors distinguish between two forms of rheumatoid iritis, the one acute, the other recurrent or chronic. The acute kind can affect one or both eyes, while the chronic type affects both eyes. Although the acute form of rheumatoid arthritis is generally associated with, or follows, joint symptoms, it may precede them by as much as one to four years. They report that Birkbeck and co-workers[220] found that thirteen out of 148 patients suffering from ankylosing spondylitis had an associated iritis. The chronic form of rheumatoid arthritis is usually found in the more severe cases of rheumatic disease. Bilateral iritis among patients having juvenile rheumatoid arthritis (Still's disease) responds poorly to the standard methods of treatment, with band keratopathy and cataracts often developing. Reiter's syndrome may also have recurrent iritis. Joint and eye manifestations can, in due time, develop into a characteristic rheumatoid disease, and the authors also reported a case of gouty iritis that would flare up during exacerbation of joint disease. These investigators report that ocular manifestations in rheumatic fever, being of an infectious origin, are a rare occurrence. Cases of brucellar arthritis and uveitis are likewise very rare. Several cases of uveitis in patients having remote tuberculosis joint diseases have been observed, but there did not seem to be any casual relationship. The authors emphasize the importance of searching for signs of associated joint disease in acute or recurring cases of iritis.

Since repeated attacks of iritis, iridocyclitis, and chorioretinitis often result in blindness, considerable interest has been focused on these diseases. Many of these cases are undoubtedly due to bacterial allergy, some being associated with a focus of infection in some other part of the body.

Behrens and his group[211] emphasize the difficulties of finding the specific bacteria or their products in lesions of the uveal tract, since demonstrating hypersensitivity of organisms in the eyes may be dangerous. As a result, skin tests must be given, but because these are often inconclusive, the diagnosis must sometimes be made on the basis of clinical experience. All possible corollary evidence should be evaluated, and Behrens and his co-workers find that coliform organisms cultured from the feces or the respiratory tract often play an important role in these cases. In their experience, such patients improve more rapidly when desensitized with autogenous coliform vaccines than when given other types of treatment.

It is now an established fact that non-granulomatous uveitis may complicate certain viral diseases, such as mumps, influenza, herpes zoster, and that "certain aspects of the clinical course of such uveitis indicate that the reaction may be, at least in part, a manifestation of viral allergy." Coles cites the work of Selzer,[221] who claims to have isolated a virus from the chorioretinal fluid and blood in Behcet's syndrome. When microbial hypersensitivity is the etiology, the streptococcus evidently is the most common cause of non-granulomatous endogenous uveitis. Coles, besides citing the evidence that exists for and against streptococcal allergy, also briefly reviewed the experimental work done, which "in man indicates that anterior uveitis is unassociated with any local bacterial infection."

The work of Leopold and Dickenson[222] provides evidence for streptococcal allergy, as well as indicating that anti-streptolysin serum titers in patients with non-granulomatous uveitis were higher than in a control group of normal individuals. Smith and Ashton[223] also found elevated anti-streptolysin titers among patients with non-granulomatous uveitis. Steen and Schone,[224] excluding all those giving a history of previous infection, measured the anti-streptolysin and anti-staphylococcus levels in patients having iridocyclitis and in a normal control group. They found that the anti-staphylococcus titers were about the same in both groups, but that the anti-streptolysin titers were generally 35 units higher among patients with iridocyclitis. Further evidence comes from the work of Alan Woods.[225] With intradermal skin testing, he demonstrated a specific hypersensitivity to various strains of streptococci in 89 per cent of patients having non-granulomatous uveitis. He also reported good therapeutic results with specific desensitization, using streptococcal antigens. Harley[226] likewise reported favorable results in cases of iritis and iridocyclitis. One of the arguments against the concept of streptococcal allergy is that skin tests are not necessarily an indicator of specific hypersensitivity of a particular tissue. Conversely, a negative skin test does not necessarily rule out ocular hypersensitivity. In ocular tuberculosis there is not always a correlation between the ocular inflammation and skin test sensitivity; the uveitis may be intense and the reactivity still mild. Occasionally, a mild iritis may exhibit a severe exacerbation upon skin testing, regardless of the amount of tuberculin used.

Such observations could have a similar validity as regards uveal sensitivity to streptococcal products. Only in rare instances have focal ocular reactions to streptococcal antigens been noted, and there are also pitfalls to interpretating skin tests. Not only may the non-specific ingredients of the test solution produce reactions, but reactions may also be more pronounced in fair skin subjects.[227] Furthermore, aged individuals with atopic skins may give "sluggish reactions" even when having a marked sensitivity. The amount of local histamine in the skin, as well as circulating inhibiting drugs,[227] may also affect the testing. Misleading non-specific skin reactions occur frequently and the reaction may, at times, "be due entirely to the particular nature of the organism apart from its specificity and may give rise to false positive results."[209] Because of the complex antigenic mosaic structure of the bacteria, determining the specific antigenic fraction to which the patient is sensitive becomes a complicated process. As a result of all these difficulties, the clinical significance of positive skin reactions to streptococcal antigens is dependent on subjective interpretations. Moreover, Lawrence[228] elicited positive skin reactions to various streptococcal fractions in a fairly large portion of a random hospital population. And although it is an established fact that the incidence of positive skin reactions to streptococcal products increases with the age of the population. Coles[209] finds it quite remarkable that we do not discover more cases of non-granulomatous uveitis among young people having rheumatic heart disease and glomerulonephritis, if the streptococcal allergy is responsible for such cases.

Because of the spontaneous exacerbations and remissions that occur, it is also difficult to evaluate desensitizing procedures as applied to uveitis. Suitable controls are hard to establish, but despite these arguments against a streptococcal allergy in uveitis, Coles finds that "there is much suggestive experimental and clinical evidence supporting the assumption that the pathogenesis of uveitis is most likely linked to streptococcal hypersensitivity."

At present, however, the precise tools and quantitative methods necessary to establish this concept with certainty are lacking. "The fact that patients with non-granulomatous uveitis have elevated anti-streptolysin titers is *prima facie* evidence that they have recently had some streptococcal disease and suggests some relationship between a recent streptococcal infection and non-granulomatous uveitis."

In his annual review of the uveal tract, Wadsworth[229] reports that European investigators[230] have also found high anti-streptolysin titers in patients with streptococcal infections. "Such a test should be valuable in determining the etiology of some cases of iritis." Stanworth, McIntyre and their investigators[231] studied 237 patients with uveitis, most of whom had an associated paradontal or nasal sinus infection. Hemolytic streptococci were found in their nose and throat cultures, while some positive pneumococci cultures were found among younger patients. Venereal disease and sarcoidosis were seldom the etiologic factor. Sugahara[232] studied 120 cases of anterior retinochoroiditis and found most of them to be due to tuberculosis. According to Wadsworth,[229] "such a preponderance may be present in Japan, but elsewhere in the world the large group allotted to tuberculosis has gradually decreased with the improvement of our diagnostic acumen." Miller and Schmerz[233] reported the interesting case of a patient who developed a severe local and systemic reaction one day after receiving an intradermal tuberculin test. Although bilateral posterior uveitis developed after sixteen days, it subsided a month later. Dworetzky[234] reported a case of bilateral uveitis due to staphylococcal allergy in which marked immediate and delayed skin reactions could be elicited to staphylococcal products. After the focus of infection was removed, the patient received vaccine therapy as well as steroids. Dworetzky believed that the vaccine therapy was an important factor in achieving a favorable therapeutic result.

At the Seventeenth International Congress of Ophthalmology, Ashton[235] objected to Woods' classification of uveitis since the histologic reactions of acute or chronic inflammation have no sharp differentiation. He also feels that too much interest has been centered on the direct allergic mechanisms of organisms, such as the streptococcus and tubercle bacillus, and that other endogenous factors may play a major role. Both the injury of circulating antibodies and the combination with bacteria and/or their products could alter the host's proteins and produce an inflammatory reaction, either through forming auto-antibodies or by directly stimulating a "foreign-body" reaction. Ashton[235] studied 200 uveitis cases and found that in anterior uveitis there was a closer association with anti-streptolysin titers and skin sensitivity to tuberculoprotein than in posterior uveitis. Posterior uveitis cases more often showed serologic findings suggestive of Toxoplasma infection.

Selecting fifty-eight patients with uveitis in order to do a complete survey, Woods and Stone[236] found no undue incidence of clinical or subclinical collagen disease. Cases of retinitis and optic neuritis, as delayed type allergies due to foci of infection or tuberculoprotein products, have also been reported.

With the advent of specific antibacterial therapy against *M. tuberculosis,* as well as with isoniazid and such drugs as paraminosalicylic acid, desensitization with tuberculin is used only infrequently. In an editorial in the *American Journal of Ophthalmology,* Woods[237] not only discusses the present status of desensitization therapy in ocular tuberculosis, but also asks whether "tuberculin still has a place in the treatment of ocular

tuberculosis or whether in the light of new developments it should be abandoned and forgotten." He calls attention to the fact that no toxic component has ever been isolated from the tubercle bacillus which does not produce an exotoxin. Following infection of a previously normal tissue, a minor inflammatory reaction at first takes place. Then there is an increased resistance to the infection, with the tissues simultaneously becoming hypersensitive to the specific protein of the bacillus. After this, a reaction between the sensitized tissues and the specific antigen (the protein fractions of the bacilli) occurs. This is associated with acute inflammation and, depending on the amount of the bacilli, necrosis, and caseation. This is the destructive phase of the tuberculous lesion, for the principle underlying tuberculin desensitization is the removal of the dangerous tissue hypersensitivity. Resistance to infection remains unchanged. Moreover, desensitization can depress or abolish hypersensitivity to such a degree that contact of the tissues with the products of the living bacilli does not produce a reaction sufficient to cause secondary inflammatory lesions in the desensitized tissues. Antibacillary therapy in tuberculosis is not, however, 100 per cent effective, as complete destruction of all bacilli is not always achieved. "Since recurrences of ocular tuberculosis," writes Woods, "do occasionally occur even after prolonged antibacterial therapy, and since tuberculin desensitization, properly administered, is a harmless form of treatment and may be given concurrently with the anti-bacterial therapy, it would appear unwise to consign this proven and time-honored treatment to the limbo of obsolete therapeutic procedures." As an adjuvant to anti-bacterial therapy, tuberculin desensitization is a justified procedure.

Leopold[238] suggests desenstitizing to tuberculin, as well as giving chemotherapy concomitantly, when treating uveitis. Although steroid therapy can frequently be used alone, he admits that "this is not fundamental and does not remove the cause." Gray[239] recommends low dosage desensitization as a concomitant form of therapy in tuberculous iridocyclitis, but tuberculin must be given cautiously to avoid an acute flare-up of iritis. Desensitization has also been reported to activate tuberculosis.[240]

Toxoplasmosis is evidently becoming more widespread and common, and an excellent description of this disease can be found in the review of Frankel and Jacobs.[241] Because of the importance of toxoplasmosis in the etiology of uveitis, Covelli[242] studied the intradermal reaction to toxoplasmosis among 100 people in Geneva. Fifty per cent of the patients over fifteen years of age gave positive reactions, while children under fifteen rarely had positive skin reactions. The percentage of positive skin reactions did not vary considerably between men and women.

Among thirty-six cases of congenital toxoplasmosis, Hogan[243] found 20 per cent having cerebral calcification. Thirty per cent of these patients had unilateral ocular disease; 33 per cent had late relapse of congenital infection; nine of the thirty-six patients had methylene blue dye tests and negative toxoplasma skin tests. This, in his opinion, is indicative that the skin test is less reliable for diagnostic purposes than the dye test. Twenty-four of the patients had a dye test titer over 1:512, and thirty-six had titers varying between 1:128 and 1:512.

According to Lunde and Jacobs,[244] the hemagglutination test is superior to the methylene blue dye test for toxoplasmosis. It is allegedly safer and the antigen can be standardized.

Since many normal individuals have toxoplasma antibodies, no quantitative or qualitative immunologic tests can differentiate between cases of chronic ocular toxoplasmosis and such inapparent or past infections. Statis-

tical studies, however, have shown that a large proportion of chorioretinitis cases are due to toxoplasmosis. According to Frankel and Jacobs,[241] patients who fulfill the following criteria should be handled as toxoplasmic cases: (1) demonstrable evidence of present or past retinal inflammatory lesions; (2) a positive dye test for toxoplasmosis (regardless of titer) or positive toxoplasmin skin test, or both; (3) signs of a generalized infection such as disseminated tuberculosis, secondary syphilis, disseminated fungus infection, et cetera, must be excluded. Furthermore, the patient should not "show stigmata of Behcet's disease, sarcoidosis, or cytomegalic virus infection, or the violently destructive ocular lesion characteristic of nematode infection."

Frankel and Jacobs[241] point out that there is considerable evidence to show that a sizable proportion of retinochoroiditis cases are caused by toxoplasmosis, which "is the only diagnosis that has been evaluated statistically." The "conventional etiologies," such as tuberculosis, syphilis, brucellosis, leprosy, leptospirosis, crytococcosis, and sarcoidosis are responsible only in a small percentage of retinochoroiditis cases. They conclude:

> A large reservoir of undiagnosed cases exists, and the probability of unrecognized etiologic agents calls for the employment, wherever possible, of unconventional and direct diagnostic procedures, such as the culture of ocular fluids and tissues in special media, under aerobic and anaerobic conditions, as well as in animals and tissue cultures.

Goldman[245] has described a new serologic test for antibodies to toxoplasma, based upon inhibition of specific staining with fluorescent antibody. Although there was a strong parallel between this test and the methylene blue dye test, the complement fixation test for toxoplasmosis did not yield nearly as many positive tests as the inhibition test.

Having reviewed the question of the specificity of the methylene blue dye test, Kessel[246] reports the results of its use in testing serums from mice and rabbits that were inoculated with pure cultures of *Trichomonas vaginalis* and from mice and rats that had recovered from infections with *Trypanosoma cruzi.* Because these tests were consistently negative at significant titers, they support the opinion that the methylene blue test is specific for *T. gondii.* Kessel also reported comparisons of dye tests results with toxoplasmin skin test results. They showed a high correlation between tests which were negative, while a smaller correlation occurred between positive dye tests and plasmosin tests.

Kaufman[247] reports that the toxoplasmin skin test is an excellent screening test for antitoxoplasma antibodies, as it was positive in 95 per cent of patients with toxoplasma dye tests who had not had steroid therapy immediately before skin testing. In only one patient out of 200—an atopic patient reacting to all antigens—was the toxoplasmin control positive. As a result, he suggests that this control may be necessary.

Frankel[248] believes that "it is interesting to note that in man, Rhesus monkeys and guinea pigs, a delayed type of hypersensitivity may be observed three to four weeks after infection of toxoplasmosis." This factor can complicate pathogenesis, especially in relation to cyst rupture. In man, the usefulness of the toxoplasmin skin test depends on the high relation of presumed infection, as indicated by antibody measures to the dye test, and to the presence of hypersensitivity. In most rodents, hypersensitivity is not demonstrable by skin tests, but nevertheless, it appears to participate in the histogenesis of lesions. Just as in tuberculosis, or after a successful BCG vaccination, when dermal hypersensitivity may fail to appear in about 10 per cent of the cases, so toxoplasmin sensitivity is not always developed

following infection, especially in young children. A more conclusive index of past infection is the presence of antibody measured in the dye test.

Cassady's review[249] of toxoplasmic uveitis should be read by everyone interested in the subject, as well as the studies of Frankel. According to Frankel,[248] the third or chronic stage of this disease is difficult to recognize. Since the organisms are incysted, the cyst walls may be so taut that antigenic and hemotactic substances cannot escape; therefore, the cysts do not produce any inflammatory reaction. It is not possible to determine by serologic or skin tests whether the person still has the infection at this chronic stage, about which little is known, except for serum antibodies against toxoplasmin and bouts of retinochoroiditis, or granulomatous uveitis.

In discussing allergy in toxoplasmic uveitis, Coles[209] states that:

> There is some evidence that the role of allergy in the production of the actual uveitis may eventually be shown to be an important one. Since the condition is predominantly a retinal disease the choroidal inflammatory response is directed against toxins or antigens, not the infecting organism itself. Whether the process is associated with any important degree of local hypersensitivity is conjectural.

In a recent issue of the *American Journal of Ophthalmology,* Woods and Wahlen[250] reported the "results of an exploratory study on the ambiguous question of the role of histoplasmosis in the etiology of uveitis." In patients with granulomatous uveitis, they found an increased incidence of positive histoplasmin reactors, as compared to those with nongranulomatous uveitis. Of sixty-two patients, nine showed the trilogy of histoplasmin sensitivity, pulmonary calcification, and allergy to tuberculin. Concerning the etiology, no cause other than histoplasmosis could be found. In ten additional patients, the picture was not so clear-cut, although the ocular picture was characteristic and the "patients undoubtedly had a benign systemic histoplasmosis." The fundus picture of these cases so far has been seen only in patients who are hypersensitive to histoplasmin. Woods and Wahlen, nevertheless, see sufficient justification to "assume a cause-and-effect relationship between a benign systemic histoplasmosis and these ocular lesions." Such a relationship occasionally exists between histoplasmosis and nongranulomatous iridocyclitis.

EXPERIMENTAL

Okumoto and his group[251] studied corneal response to repeated inoculation with herpes simplex virus in rabbits. Systemic immunity associated with circulating antibodies did not offer protection against corneal infection by the virus, although there was some resistance to reinfection after corneal infection by the virus. This was believed to be due to a strain-specific characteristic rather than to circulating antibodies.

Along the same line, Gispen[252] was unsuccessful in immunizing rabbits against herpes simplex keratitis both actively and passively. When giving the virus intravenously, however, he did succeed in immunizing them against herpes encephalomyelitis. In view of this, Gispen concluded that the virus has antigenic properties but does not affect the cornea because of the absence of vascularization. The organisms cannot effectively be neutralized.

On the experimental allergic reaction in the eye, there have been surprisingly few histopathologic studies, and the findings are somewhat contradictory and inadequate. In an effort to remedy this situation, Woods, Friedenwald, and Woods[237] used both bacterial and foreign protein antigens in a series of histopathologic studies, for the sensitization and reinjection of rabbits. They report that single acute allergic reactions were caused

by one anterior chamber injection, while prolonged allergic inflammation was produced by repeated anterior chamber and intravitreal injections of the specific antigens of the eyes of sensitized animals. The ocular reaction, which followed either a single or repeated allergic insult, showed the general pattern of nonspecific inflammation. No tuberculoid or granulomatous reactions appeared in the eyes of the rabbits subjected to acute or prolonged allergic inflammation, and only one eye showed a sheet of pallisating epithelioid cells suggestive of the reaction found in rheumatic or rheumatoid nodules. The authors give no explanation for this, except that it might represent a peculiar form of chronic allergic inflammation. Furthermore, they found no marked difference between ocular reactions produced in animals specifically sensitized by foreign proteins and those sensitized by bacterial antigens.

Favour[253] studied thirty-six patients with various forms of inflammatory eye disease who had been referred to the internists for a search of foci of infection. Among thirty patients on whom allergic information was complete, eight gave a history of past allergic reaction, while one additional patient had a family history of allergy. This is the same percentage as in an unselected population. Eight of the thirty-six patients showed a definite relationship of their attacks of eye disease with dental infection. According to Favour:

> Two patients in this series could not have had dental infection as the etiology of their disease—they had no teeth. . . . One patient suffered from chronic prostatitis, long antedating his iritis. . . . His chronic eye disease would flare up when his prostatitis was active. The prostatitis and eye disease subsided with autogenous vaccine treatment. Another patient had had five attacks of iritis before being studied.

Two of these attacks had followed dental procedures, but after removal of his teeth, the patient was asymptomatic for one year, the longest period he had been without relapses. Following a seasonal upper respiratory infection, this patient had a mild recurrent attack of iritis, and he had another attack later without any evidence of infection. A beta hemolytic streptococcus could be recovered from his throat and he then gave a marked positive skin test to beta hemolytic streptococcus, despite frequent penicillin treatment. Two patients had chronic bronchial infection, apparently unrelated to their eye symptoms. There were no patients in this group with a history of tuberculosis. One patient with a chronic draining empyema, from which *Staphylococcus aureus* was repeatedly isolated, suffered from a chronic staphylococcus blepharitis. Although none of the patients had a history of tuberculosis, two had experienced tuberculous contacts, and one suffered from recurrent vitreous hemorrhage. On this latter patient, the tuberculous reaction was the most marked of his skin tests, and he became asymptomatic after tuberculin treatment. The other patient, who showed multiple delayed type reactions, responded to treatment of combined brucellin and tuberculin. Three patients with uveitis and negative tuberculous histories, but with weakly positive tuberculin tests, were unsuccessfully treated with tuberculin. Infection in the gastrointestinal tract was found to be the cause of two of the chronic eye cases. When thirty-three patients were carefully questioned as to their joint symptoms, two were found to have frank rheumatoid arthritis, one gave a history of migratory polyarthritis and rheumatic disease, and ten gave past histories of incapacitating arthritis lasting for periods of one month or longer. Most of these attacks were unrelated to eye symptoms. In ten of the thirty-six patients, no clue as

to the cause of their eye disease could be found from physical examination.

In his series, Favour found that skin tests with a variety of brucellergin were useful, while antibiotics, tuberculin therapy, bacterial vaccines, and removal of foci of infection often did not prevent remissions in chronic or recurring uveitis. From a bacteriologic and immunologic point of view, eradication of infections with these methods is rarely accomplished, although this does not justify the omission of routine bacteriologic studies or skin testing to the suspected bacteria or their products. If these are not revealing, it may often be found profitable to subject the leukocytes of the patient to the filtrates of the various strains of bacteria.[254] Favour concludes, however, that with our present state of knowledge prudent use of these therapeutic methods is justified. When using streptococcal vaccine, subcutaneous injections should be given, and when using staphylococcus toxoid, intradermal injections should be given.

In an experiment with rabbits, Miescher[255] studied the relationship between trauma, infection, and tissue hypersensitivity in ophthalmia. A perforating trauma in itself did not produce "hypergic" uveitis in rabbits sensitized actively or passively against uveitis. It appears that various pathogenic factors, such as trauma, infection, and an immunologic process, must work together before sympathetic ophthalmia develops.

THERAPEUTICS IN OCULAR ALLERGIES OF THE DELAYED TYPE

Leopold places particular emphasis on the point that "ocular allergies due to hypersensitivity to bacteria constitute a significant problem in therapy."[238] In long-standing cases, when bacterial allergy is almost invariably present, desensitization with autogenous vaccines, as well as with all the autogenous bacterial products, is preferred over the use of commercial vaccine-toxoid combinations. Similar to the experience of Thygeson,[202] the best therapeutic results occur among patients with the most marked initial skin tests. Vaccines may be made either from the whole bacterial organism, selected antigenic fractions, filtrates, or solutions containing the endotoxin or exotoxins produced by the bacteria, or various combinations of these. Leopold also feels that, when one of the bacterial offenders cannot be identified, vaccines prepared from several organisms may be used as a nonspecific therapy. Antibiotics are seldom able to eradicate the focus of infection completely, and he warns that many of these agents are bacteriostatic only when used in safe concentrations. Since the bacteria or their products are not entirely eliminated by the antibiotic, antigenic stimulation may continue. And whenever the infecting agent responsible for the disease cannot be entirely eliminated, hyposensitization or desensitization injections should be given. Leopold recommends the method of Solis-Cohen,[256] which involves the use of the patient's whole fresh blood for killing organisms to which he is immune, thus permitting the growth of potential pathogens. Ridley and Harley[257] agree with this method of selecting allergens for bacterial sensitization, for toxoid is generally more successful in treating subacute or chronic infections.[189,202,258]

Although Theodore[189] recommends toxoids and vaccine therapy in treating infectious eczematoid staphylococcal dermatitis of the eyelids, he feels that the antigenic properties of toxoid for producing antitoxoid are superior to those of vaccines. The immunity is antitoxic, not antibacterial, and vaccines stimulate the formation of other types of antibodies, with no antitoxin being formed. The initial dosages should be determined individually by the reactions to small intradermal injections. When staphylococcus

toxoid is used, the original injection should be 0.01 to 0.02 given intradermally, and when 0.1 cc is reached, it may still be given intradermally, with the remainder of the dose injected subcutaneously. At an increase of 0.1 cc at a time, the injections are to be given four to five days apart, or weekly. They are spaced further apart when 1.0 cc is attained, although they should be maintained at that level for quite some time in order to insure a constant level of elevation of antitoxin in the blood. For maintenance, Theodore uses the dose which produces clinical improvement. Tassman[203] reports the use of a new purified toxoid, whereby maximal titers are reached after only a few injections and maintained regardless of the time interval between injections. In most cases, Leopold does not consider surgical removal of a focus to be a desirable therapeutic method.[238] When it is performed, however, it should be accompanied, and if possible preceded, by desensitization.

SYMPATHETIC UVEITIS AS AN ALLERGIC PHENOMENON

Ever since Elschnig's article appeared in 1908, more and more ophthalmologists have accepted the concept that sympathetic uveitis has an allergic component. Today, many investigators believe that a bacterial allergy is superimposed onto an allergy to uveal tissue in this disease. Streiff and Miescher[259] gave convincing evidence that certain virus infections occur much more violently and extensively in animals sensitized to uveal tissue. On the contrary, Blodi,[260] in reviewing the development and present status of the allergic theory of sympathetic uveitis, states that these factors are not the cause of sympathetic uveitis, but "merely set the stage for another, perhaps infectious, factor." He points out that, in addition to uveal pigment, the role of the foreign protein sensitivity has been evaluated repeatedly, and that when trauma is added to such sensitization, the resulting uveitis in animals may be strikingly similar to sympathetic uveitis. Blodi[260] also calls attention to the fact that this disease frequently occurs together with phacoanaphylactic endophthalmitis, in which auto-sensitization is also a factor. Moreover, it may be a bilateral disease characterized by typical granulomatous reaction. According to Blodi, if it could be proven that this coincidental occurrence is more frequent than could be expected by a random association, we would have "additional weight of evidence to the allergic theory of sympathetic uveitis." In 170 cases of eyes with sympathetic ophthalmia, thirty-nine also showed a phacoanaphylactic reaction. Since this is more frequent than could be expected by chance coincidence, Blodi suspects that the two conditions might influence each other.

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(To be continued)

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Each, of twenty-nine children, was given 0.15 ml of gamma globulin per pound of body weight (0.05 gm per kg). Twenty-three patients responded favorably, fourteen being completely asymptomatic, while nine suffered rare mild wheezing of a few hours duration. Only six patients continued to have asthma.

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Topical use of Veriderm Medrol Acetate produces symptomatic relief and objective improvement of dermatoses, and at the same time aids in correcting dry skin conditions. Veriderm Medrol Acetate, less greasy than an ointment and less drying than a lotion, is indicated in atopic, contact, or seborrheic dermatitis, and in neurodermatitis, anogenital pruritus, and allergic dermatoses.

Available in four formulations: Veriderm Medrol Acetate 0.25% – Each gram contains: Medrol (methylprednisolone) Acetate 2.5 mg.; Methylparaben 4 mg.; Butyl-p-hydroxybenzoate 3 mg.; in a skin lipid base composed of saturated and unsaturated free fatty acids; triglycerol and other esters of fatty acids; saturated and unsaturated hydrocarbons; free cholesterol; high-molecular-weight alcohol; with water and aromatics. (Veriderm Medrol Acetate 1% is also available.)

For prophylaxis against secondary infection: Veriderm Neo-Medrol Acetate 0.25% – Each gram contains: Medrol (methylprednisolone) Acetate 2.5 mg.; Neomycin Sulfate 5 mg. (equivalent to 3.5 mg. neomycin base); Methylparaben 4 mg.; Butyl-p-hydroxybenzoate 3 mg.; in a skin lipid base composed of saturated and unsaturated free fatty acids; triglycerol and other esters of fatty acids; saturated and unsaturated hydrocarbons; free cholesterol; high-molecular-weight alcohol; with water and aromatics. (Veriderm Neo-Medrol Acetate 1% is also available.)

Administration: After careful cleansing of the affected skin to minimize the possibility of introducing infection, a small amount of either Veriderm Medrol Acetate or Neo-Medrol Acetate is applied and rubbed gently into the involved areas. Application should be made initially one to three times daily. Once control is achieved – usually within a few hours – the frequency of application should be reduced to the minimum necessary to avoid relapses. The 1% preparation is recommended for beginning treatment and the 0.25% preparation for maintenance therapy.

Contraindications: Local application of Veriderm Medrol Acetate or Neo-Medrol Acetate is contraindicated in tuberculosis of the skin and in other cutaneous infections for which an effective antibiotic or chemotherapeutic agent is not available for simultaneous application.

These preparations are usually well tolerated. However, if signs of irritation or sensitivity should develop, application should be discontinued. If bacterial infection should develop during the course of therapy, appropriate local or systemic antibiotic therapy should be instituted.

Supplied in 5 Gm. and 20 Gm. tubes.

Veriderm

Medrol† Acetate

Neo-Medrol† Acetate

TRADEMARK

†TRADEMARK, REG. U. S. PAT. OFF.

Upjoh

The Upjohn Company, Kalamazoo, Michi

TOPICAL STEROID NEWS:
BREAKTHROUGH IN THERAP

In steroid responsive dermatoses yo
may prescribe new Panzalone Cream fo
rapid healing without concern about sid
effects and cost-to-patient, even whe
used on extensive areas for prolonge
periods.

2% CREA

PANZALONE™

delta-5-hemisuccinoxypregnenolone*, DOA

BREAKTHROUGH IN THERAP

because the 2% concentration of Panzalone Crea
helps assure quick relief of symptoms and mor
rapid healing of lesions,

because Panzalone is a new and fundamentall
different steroid for topical application; it is non
corticoid and thus cannot produce corticoid side
effects and

because cost-to-patient of an Rx for Panzalone
Cream, reflecting the economies in synthesis o
this new steroid, will be less than ½ the average
for comparable topical steroid creams.

Panzalone Cream is applied 3-4 times a day, supplied as 15 Gram (½ oz.) tubes. Each gram of water washable crea
contains 20 mg. of delta-5-hemisuccinoxypregnenolone
(△5-prègnen-3(β)-hemisuccinoxy-20-one), DOAK wit
Buro-Sol®, DOAK (equivalent to 3.38 mg. aluminum acetate
pH 5.5. Distributed in Canada by Trans-Canada Pharmaca
Co., Montreal, P. Q.

*PATENT PENDI

DOAK Pharmacal Co., Inc., New York 16, N.Y.

Even if you had only one asthma patient in your practice, chances are you would need more than one kind of antiasthmatic preparation to manage the variable problems this patient presents.

But because allergy is your specialty . . . and you undoubtedly treat many patients with asthma . . . *chances are you need a full line of antiasthmatic preparations to meet each patient's demands for variable therapy.*

Neisler antiasthmatic products are formulated to provide you with a flexible program of asthma therapy that can be adjusted to each individual's requirements for emergency relief of the acute attack . . . sustained relief of chronic asthma . . . and prophylaxis.

AND YOUR PATIENTS GET THE ADDED BENEFITS OF "PROTECTED AMINOPHYLLINE."*

Neisler's Dainite and Cardalin preparations utilize "protected aminophylline," a unique addition of protective factors that permit rapidly achieved and sustained therapeutic blood levels. Thus safeguarded, prolonged oral administration of therapeutically effective doses is possible with a minimum of gastric disturbances.

This protection is an exclusive, patented feature.* It enables you to have full confidence in the effectiveness and safety of the Neisler "protected aminophylline" preparations you prescribe for asthma sufferers.

in Asthma...

you have a choice of therapy

because a choice is vital

No single agent can control all aspects of asthma...

The Neisler line of antiasthmatic products gives you the latitude of choice you need.

DAINITE® PEDIATRIC TABLETS*

Exclusively for the child with asthma. Provide 24-hour protection with relief of bronchoconstriction, marked increase in vital capacity and minimum incidence of gastric side effects.

Aminophylline	1 gr.
Ephedrine HCl	1/12 gr.
Phenobarbital	⅛ gr.
Ethyl aminobenzoate	⅛ gr.
Aluminum hydroxide	½ gr.

Age 2-6 yrs., 1 tablet at 8 a.m., 4 p.m. and at bedtime; 7-12 yrs., 2 tablets at 8 a.m., 4 p.m. and at bedtime. Or, as directed by the physician.

DAINITE® DAY TABLETS*

Especially adjusted to provide optimal therapeutic benefits during the waking hours.

Sodium pentobarbital	¼ gr.
Aminophylline	3 gr.
Ephedrine HCl	¼ gr.
Ethyl aminobenzoate	¼ gr.
Aluminum hydroxide	2½ gr.

1 tablet on arising and 1 tablet at 4 p.m. If this does not give patient complete or prolonged relief, the dose should be changed to 1 or 2 tablets before each meal.

DAINITE® NIGHT TABLETS*

Especially adjusted and modified to provide balanced therapeutic benefits while the patient sleeps.

Phenobarbital	⅜ gr.
Sodium pentobarbital	½ gr.
Aminophylline	4 gr.
Ethyl aminobenzoate	¼ gr.
Aluminum hydroxide	2½ gr.

1, 1½ or 2 tablets—depending on the patient's requirements—at 10 p.m.

DAINITE®-KI TABLETS*

For greater protection against asthmatic attacks and for relief of dry wheezing cough. Provide extra bronchial dilation; guard against gastric irritation; calm the patient.

Potassium iodide	5 gr.
Aminophylline	3 gr.
Phenobarbital	¼ gr.
Ephedrine HCl	¼ gr.
Ethyl aminobenzoate	¼ gr.
Aluminum hydroxide	2½ gr.

1 tablet on arising, 1 tablet at 4 p.m. and 1 or 2 tablets at bedtime.

CARDALIN® TABLETS*

For maximum safety in the effective management of emphysema. Doubly protected aminophylline produces therapeutic blood levels. Supply two protective factors to successfully minimize gastric side actions.

Aminophylline	5 gr.
Aluminum hydroxide	2½ gr.
Ethyl aminobenzoate	½ gr.

2 to 4 tablets in divided dosage after meals. Start the patient on 1 tablet after the morning meal and 1 tablet after the evening meal. Build up the daily dosage at the rate of 1 additional tablet per day, preferably with one-half glassful of milk.

CARDALIN-PHEN® TABLETS*

All the benefits of Cardalin antiasthmatic therapy plus sedative action to calm anxiety and agitation.

Aminophylline	5 gr.
Aluminum hydroxide	2½ gr.
Ethyl aminobenzoate	½ gr.
Phenobarbital	¼ gr.

Follow dosage directions for Cardalin tablets.

KI-N® TABLETS

Convenient, accurate administration of potassium iodide for liquefying secretions and promoting drainage of the upper respiratory tract.

Potassium iodide	10 gr.

Equal to 10 minims of saturated solution.

1 tablet 3 or 4 times daily.

DYLEPHRIN® ORAL INHALANT

The only stable preparation of its kind available. A combination of two synergistic antiasthmatic drugs for aerosol therapy.

Each 100 cc. contains:

Epinephrine HCl (synthetic racemic)	2.5%
Atropine sulfate	0.5 Gm.

Place 8-10 drops in a nebulizer; inhale mist until relief is achieved. Repeat procedure as directed by the physician. Number of inhalations usually required to obtain relief will vary between 4 and 8 for each administration, so that patient actually employs from 0.1 to 0.4 cc. of Dylephrin.

*The unique difference in these prescription drugs is attested to by the following U. S. patent: No. 2,667,439. They are not duplicated.

IRWIN, NEISLER & CO. *75TH YEAR • DECATUR, ILLINOIS*

in severe drug and food sensitivity... rapid relief and control of symptoms on short-term therapy with Decadron®

treatment with DECADRON – orally or parenterally – can provide rapid and effective control of allergic emergencies and acute allergic disorders as reactions to foods, drugs, plants, weeds, and animals. In 40 patients given Injection DECADRON Phosphate, "subjective improvement was often d within one hour and objective improvement recorded within 4 hours."[1] Therapeutic doses of steroids may help prevent recurrences of severe ic states, without interfering with desensitization or other immunity procedures.[2]

prescribing or administering DECADRON, the physician should consult the detailed information accompanying the package or available on request.

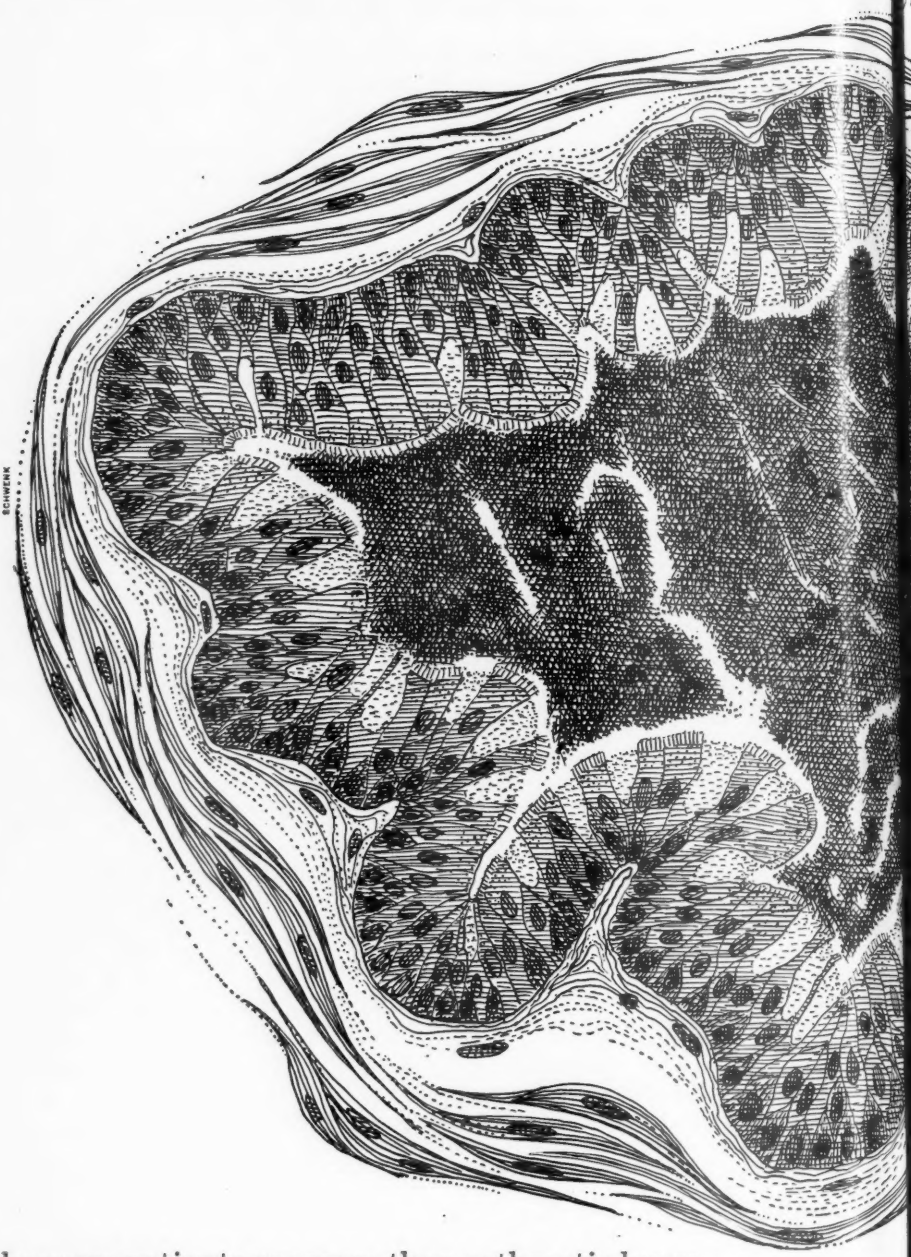
ces: 1. Grater, W. C.: Southern M. J. 53:1144, 1960. 2. Feinberg, S. M.: Med. Sci. 6:(No. 3) 959.

d: As 0.75 mg. and 0.5 mg. scored, pentagon-shaped tablets in bottles of 100 and 1000. ection DECADRON Phosphate in 5 cc. vials, each cc. containing 4 mg. of dexamethasone 21- ate as the disodium salt; inactive ingredients: 8 mg. creatinine, 10 mg. sodium citrate; hydroxide to pH 7.8, and water for injection q. s. 1 cc.; preservatives: 0.32 per cent sodium e and 0.5 per cent phenol. DECADRON is a trademark of Merck & Co., Inc.

MERCK SHARP & DOHME Division of Merck & Co., INC., West Point, Pa.

decadron®

DECADRON: Recommended dosage schedule in the treatment of drug and food sensitivity reactions		
time	amount	administration
1st day	one to two cc. (4 to 8 mg.) Injection DECADRON Phosphate intramuscular	repeated as necessary (In substituting tablet therapy, give the first oral dose four or five hours before the final parenteral dose.)
2nd day	two 0.75 mg. Tablets DECADRON	b.i.d.
3rd day	two 0.75 mg. Tablets DECADRON	b.i.d.
4th day	one 0.75 mg. Tablet DECADRON	b.i.d.
5th day	one 0.75 mg. Tablet DECADRON	per day
6th day	one 0.75 mg. Tablet DECADRON	per day
7th day	RETURN VISIT	



because patients are more than asthmatic lungs...

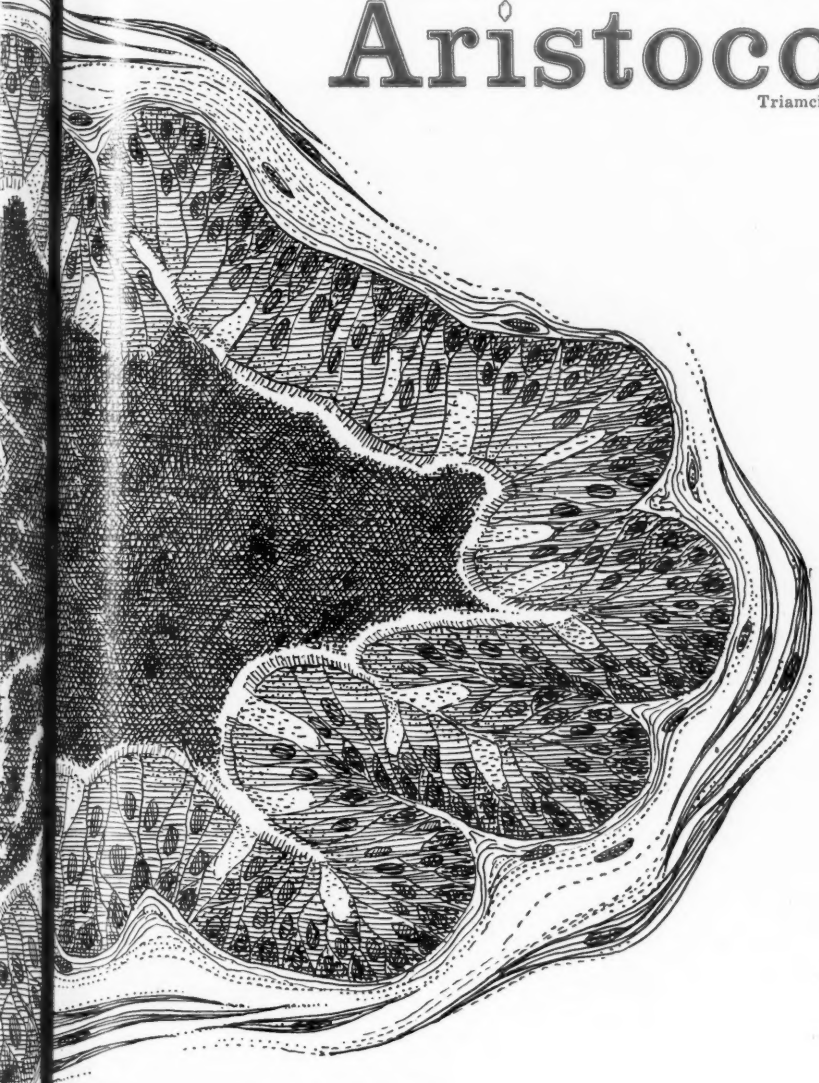
controlling inflammatory symptoms is frequently not enough!

Even cortisone, with its severe hormonal reactions, can effectively control inflammatory symptoms in bronchial asthma. But a patient is more than the sum of his parts – and the lung is only part of a whole patient. Symptomatic control is but one aspect of modern corticotherapy, because what is good for the symptom may also be bad for the patient.

Unsurpassed "General Purpose" and "Special Purpose" Corticosteroid...
Outstanding for Short- and Long-Term Therapy

Aristocort®

Triamcinolone Lederle



(Cross-section of asthmatic bronchiole; lumen filled with exudate)

ARISTOCORT is an outstanding "special purpose" steroid when the complicating problem is increased appetite and weight gain, sodium retention and edema, cardiac disease, hypertension or emotional disturbance and insomnia.

ARISTOCORT provides unsurpassed anti-inflammatory control without sodium retention or edema — without undesirable psychic stimulation and voracious appetite.

Supplied: Scored tablets (three strengths), syrup, parenteral and various topical forms. Request complete information on indications, dosage, precautions and contraindications from your Lederle representative, or write to Medical Advisory Department.

Lederle LEDERLE LABORATORIES • A DIV. OF AMERICAN CYANAMID COMPANY • PEARL RIVER, N. Y.

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Only ALGIC and new ALGIC-S.A. provide three essential effects in a single tablet...

ALGIC®

NEW ALGIC–S.A.

Sustained Action

Antihistaminic / tranquilizer / decongestant

The comprehensive therapy for the allergic patient

— prevents allergic manifestations
— allays patient anxiety
— decongests swollen tissues

"The very nature of the formula predicts its effectiveness in allergic diseases."[1]

"Algic is highly effective in symptomatic therapy."
"82% experienced marked therapeutic effect."[2]

Usual Adult Dosage:

Algic	1 to 2 tablets every 4 hours.
Algic-S.A.	1 tablet every 8 to 10 hours.

Children (6-12): one-half adult dosage.

Each scored tablet contains:	Algic	Algic-S.A.
Chlorpheniramine Maleate	3 mg.	6 mg.
Phenyltoloxamine Dihydrogen Citrate	50 mg.	100 mg.
Racephedrine Hydrochloride	30 mg.	60 mg.

(1) St. John, M. A., Shure, N. and Gaynes, H. E., "Appraisal of a New Anti-Allergy Compound", Ann. Allergy 19:157, 1961. (2) Swartz, H., "Clinical Evaluation of a New Drug (Algic) in the Symptomatic Therapy of Perennial Allergic Coryza" Curr. Ther. Res. 2:327-332, 1960.

SPENCER Laboratories, Inc., Morristown, New Jersey

If "jitters" limit dosage for your ASTHMA patien

℞

EPHOXAMINE®

Bronchodilator/tranquilizer

TABLETS – PEDIATRIC SYRUP

—provides full bronchodilator potency
—1/6th of the CNS stimulation liability

The bronchodilator actions of Racephedrine and Ephedrine are equal.[2]
The clinical (official) doses are the same.

Pharmacological studies by Schulte, et al[3] in which the central excitatory effects of Racephedrine and Ephedrine are compared show *Racephedrine has 1/6th the central nervous system side-effects liability of Ephedrine.*

"Ephoxamine has been found to be a *highly useful asthmalytic* preparation, which seems to be effective when the usual, oral asthmalytics are not." [1]

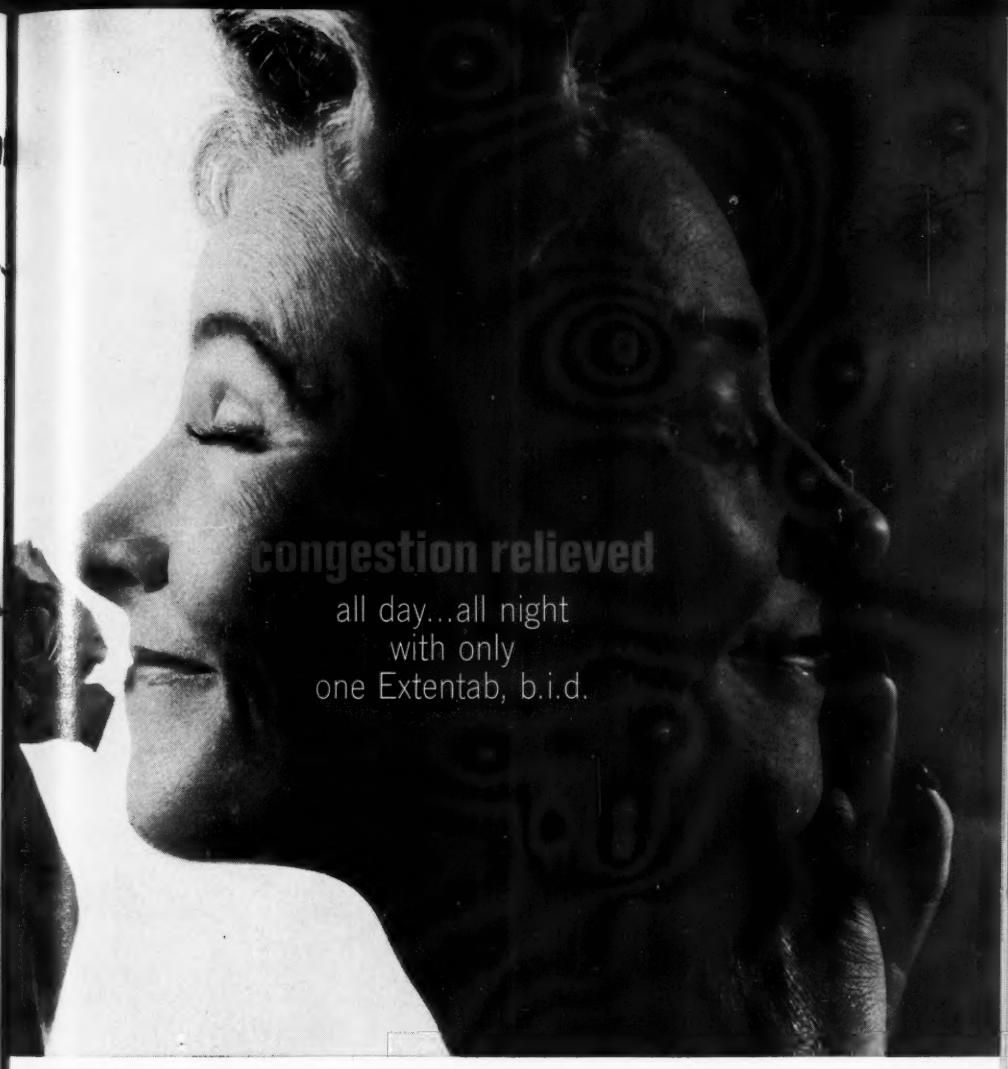
Suggested Dosage: Syrup — Children 2-4 yrs., ½-1 tsp.; 4-7 yrs., 1-2 tsp. every 4 hours. Tablets (scored) — Children 6-12 yrs., ½-1 tablet; Adults 1-2 tablets every 4 hours.

One tsp. of syrup is equal to ¼ tablet. Each scored tablet contains: 50 mg. Phenyltoloxamine DHC and 30 mg. Racephedrine HCl.

Contraindications: Usual care in the use of sympathomimetics in patients with hypertension, hyperthyroidism, diabetes, and heart disease should be exercised.

1. Swartz, H., "Ephoxamine in the Symptomatic Therapy of Bronchial Asthma" Current Therapeutic Research, 1:3; Nov. 1959.
2. Goodman and Gilman, "The Pharmacological Basis of Therapeutics" the Macmillan Company, 1958.
3. Schulte, J. W., Reif, E. C., Bacher, Jr., J. A., Lawrence, W. S., and Tainter, M. L., J. Pharmacol. Exp. Ther., 11:62-74.

SPENCER Laboratories, Inc., Morristown, New Jersey



NEW

Dimetapp® Extentabs®

let your sinusitis, allergy and U.R.I. patients breathe easier!

DIMETAPP Extentabs contain Dimetane®(parabromdylamine [brompheniramine] maleate) 12 mg., phenylephrine HCl 15 mg., and phenylpropanolamine HCl 15 mg., a proved antihistamine and two outstanding decongestants. The dependable Extentab form provides sustained relief from the stuffiness, drip and congestion of sinusitis, colds and U. R. I. for 10-12 hours with a single dose.

A. H. ROBINS CO., INC. RICHMOND 20, VIRGINIA

MAKING TODAY'S MEDICINES WITH INTEGRITY SEEKING TOMORROW'S WITH PERSISTENCE

Medrol... (methylprednisolone) a form for every use

MEDROL* TABLETS
2 mg. in bottles of 30 and 100
4 mg. in bottles of 30, 100 and 500
16 mg. in bottles of 50

SOLU-MEDROL*
40 mg. in 1 cc. Mix-O-Vial*

MEDROL MEDULES*
4 mg. in bottles of 30, 100 and 500 capsules
2 mg. in bottles of 30 and 100

DEPO-MEDR... WITH ...RTHO...ABLE
40 mg./... in 1 cc.
5 cc. via...
20 mg./... in 5 cc.
...bottles

EDROL
ITH
RTHOXINE*
ABLETS
bottles of 30 and 100

VERIDERM†
MEDROL acetate
AND
NEO-MEDROL* acetate
0.25% and 1%
in 5- and 20-Gm.
tubes

MEDAPRIN*
TABLETS
in bottles of 100
and 500

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†Trademark

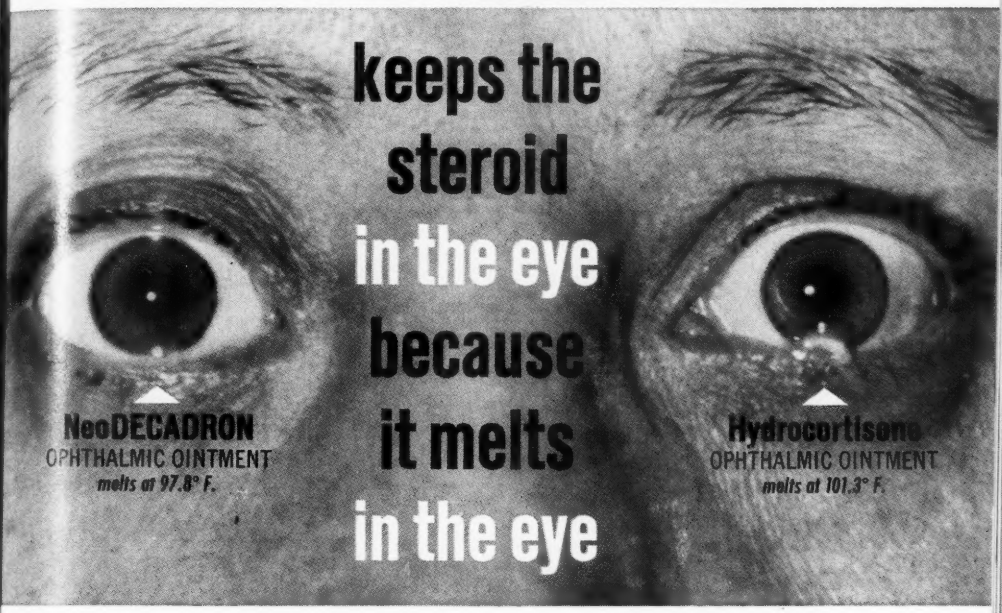
September, 1961

The Upjohn Company, Kalamazoo, Michigan

Upjohn
75th year

NeoDecadron®

DEXAMETHASONE 21-PHOSPHATE—NEOMYCIN SULFATE **OPHTHALMIC OINTMENT**



FOR:

GREATER EFFECTIVENESS—NeoDECADRON Ophthalmic Ointment melts at body temperature . . . providing optimal coverage of optimal concentration at the site of the lesion—it does not "pop out" on the lid.

ACTIVITY—dexamethasone 21-phosphate for unexcelled topical activity and solubility plus neomycin sulfate for broad antibiotic protection.

CONVENIENCE—in addition to NeoDECADRON Ophthalmic Ointment, NeoDECADRON® Ophthalmic Solution is available—a dosage form for every need.

INDICATIONS: Trauma—mechanical, chemical or thermal; inflammation of the conjunctiva, cornea, or uveal tract involving the anterior segment; allergy; blepharitis.

PRECAUTION: Steroid therapy should never be employed in the presence of tuberculosis or herpes simplex.

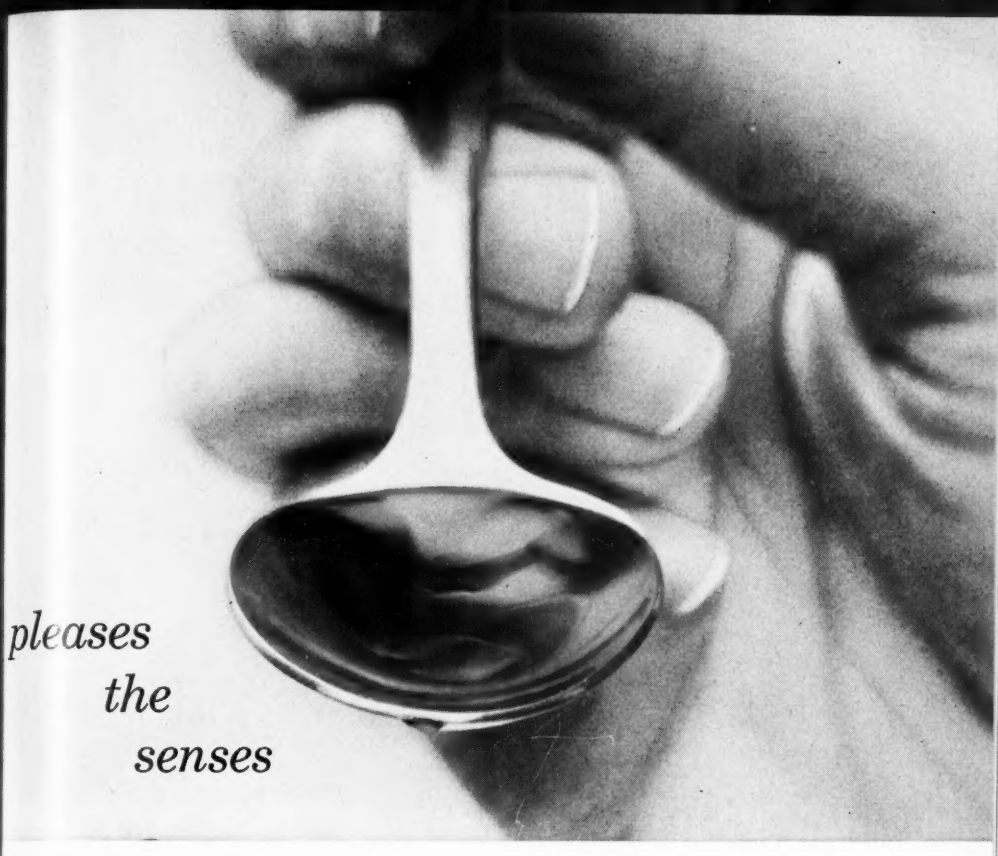
Before prescribing or administering NeoDECADRON Ophthalmic Ointment or Solution, the physician should consult the detailed information on use accompanying the package or available on request.

DOSAGE: Ophthalmic Ointment: Instill three or four times daily. Ophthalmic Solution: One drop four to six times daily. Dosage may be adjusted up or down, depending upon the severity of the disorder.

SUPPLIED: The ointment is supplied in 3.5 Gm. (⅛ oz.) tubes. Each Gm. contains 0.5 mg. of dexamethasone 21-phosphate as the disodium salt and 5 mg. of neomycin sulfate (equivalent to 3.5 mg. neomycin base). Also contains white petrolatum and liquid petrolatum. The solution is supplied in 2.5 cc. and 5 cc. sterile bottles with dropper assembly. Each cc. contains 1 mg. dexamethasone 21-phosphate as the disodium salt, 5 mg. neomycin sulfate (equivalent to 3.5 mg. neomycin base). Inactive ingredients: creatinine, sodium citrate, sodium borate, polysorbate 80, sodium hydroxide (to adjust pH) and water for injection. 0.32% sodium bisulfite and 0.02% benzalkonium chloride added as preservatives.

NeoDECADRON is a trademark of Merck & Co., INC.

MERCK SHARP & DOHME Division of Merck & Co., INC., West Point, Pa.



...as it eases the respiratory allergy

NORISODRINE® syrup

with calcium iodide

Whether he's afflicted with allergic sniffle or outright asthma, a cooperative patient can mean half the battle. That's why a treatment that's no chore to take can be so important. And that's what you get in Norisodrine Syrup.

You'll find, first, with Norisodrine Syrup a bronchodilator-expectorant useful in controlling a wide range of respiratory allergies. You'll *also* find that there's nothing easier on the senses than Norisodrine Syrup—golden color, fresh mint taste, pleasant smell.

Time and again, Norisodrine Syrup's value has been proved in patients with chronic cough, wheeze, or other classic asthma symptoms.

In a study[1] *covering the treatment of 150 patients —ranging in age from one to seventy-three years— 133 reported good to excellent results.*

Conclusions were: "Norisodrine Syrup diminished cough, brought about easy expectoration of mucus from the bronchial tree, lessened tightness in the chest, improved respiration."

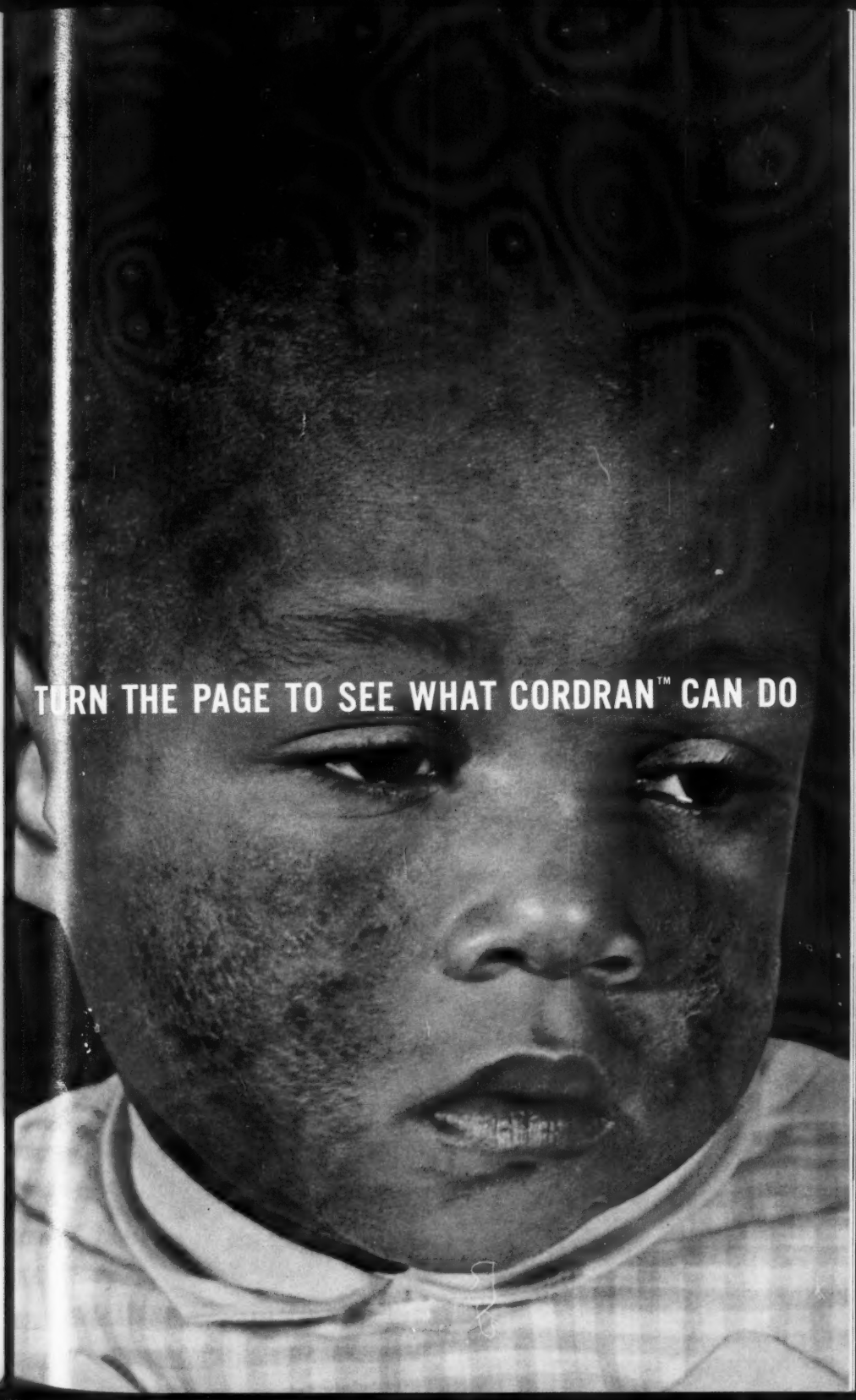
Consider good-tasting Norisodrine Syrup for your next respiratory allergy patient. It can help you manage symptoms that have been troublesome for years.

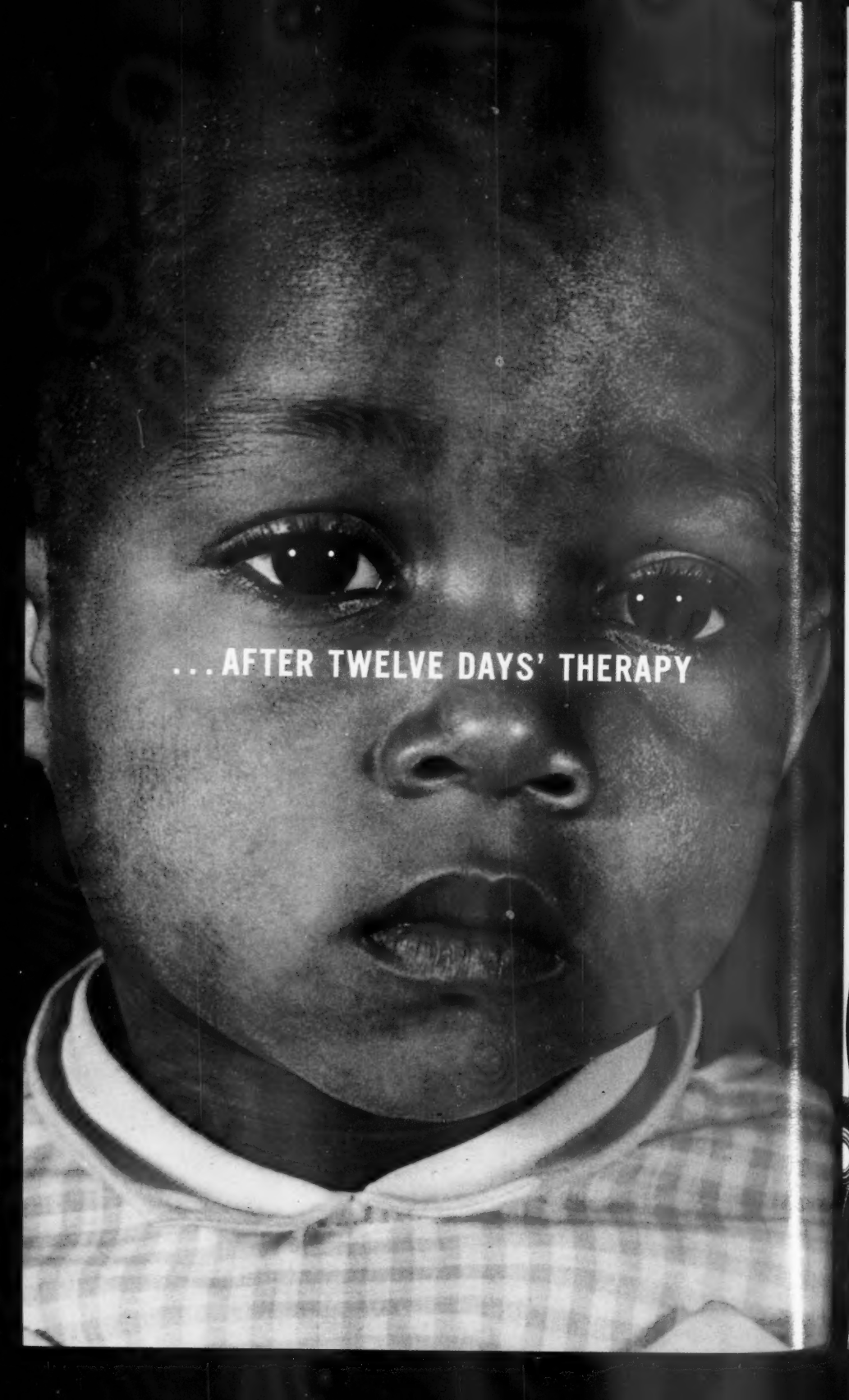
[1]Frohman, I. P., A New Antitussive Agent, M. Times, 88:924, Aug. 1960.

Norisodrine: Isoproterenol Sulfate, Abbott.

ABBOTT

100461


TURN THE PAGE TO SEE WHAT CORDRAN™ CAN DO


. . . AFTER TWELVE DAYS' THERAPY

Lilly

new topical corticosteroid

CORDRAN™

provides effective antipruritic and anti-inflammatory activity

Among the advantages:

• high effectiveness in low concentration • specific topical action • no evidence of systemic absorption with ten to twenty times the usual dosage

...and to combat infection

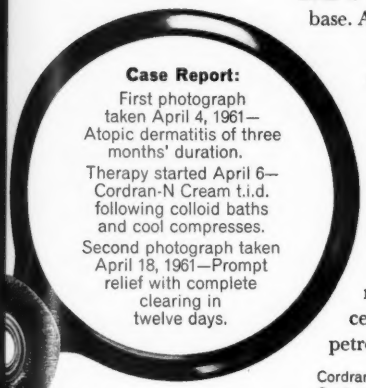
CORDRAN™-N

Cordran-N combines Cordran and the wide-spectrum antibiotic, neomycin. It is particularly useful in dermatoses complicated by potential or actual skin infections.

Product Description: Cordran and Cordran-N are available in both a vanishing cream and a hydrophilic ointment base. All forms are supplied in 7.5 and 15-Gm. tubes.

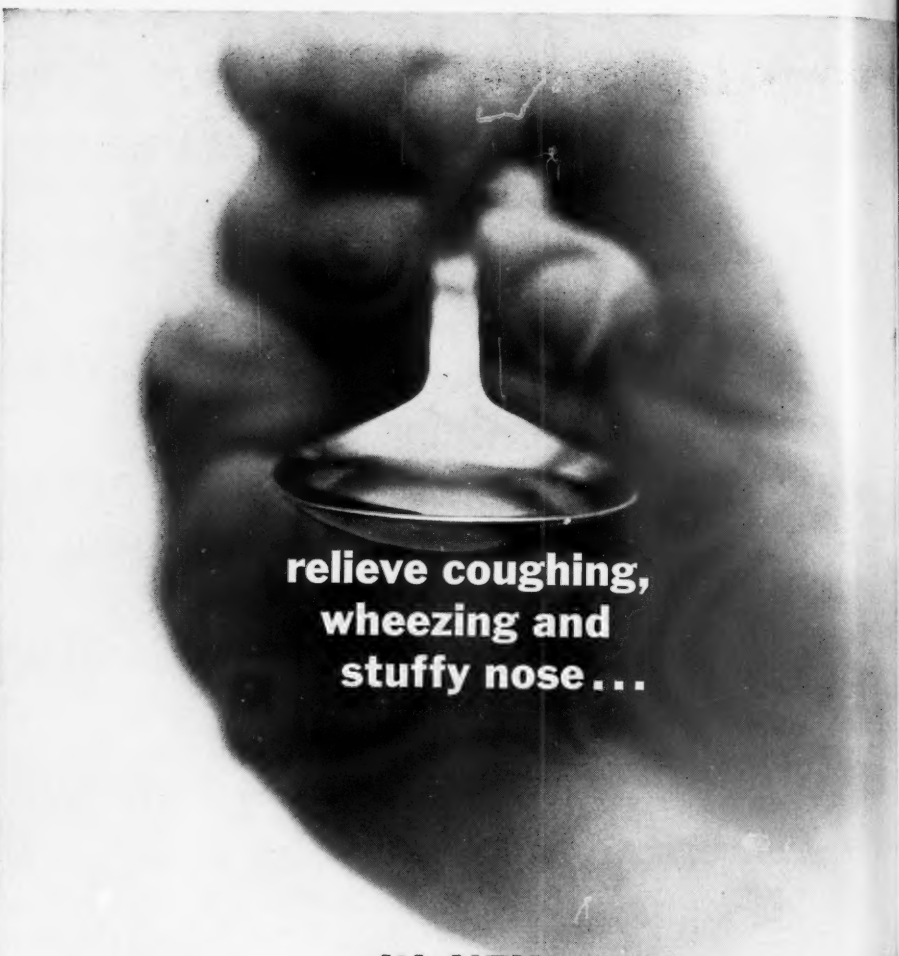
Each Gm. of Cordran cream and ointment contains Cordran, 0.5 mg. Each Gm. of Cordran-N cream and ointment contains Cordran, 0.5 mg., and neomycin sulfate, 5 mg. (equivalent to 3.5 mg. base).

The cream base is composed of stearic acid, cetyl alcohol, liquid petrolatum, polyoxyl 40 stearate, ethyl parahydroxybenzoate, glycerin, and purified water. The ointment base is composed of white beeswax, cetyl alcohol, sorbitan sesquioleate, and white petrolatum.



Cordran™ (flurandrenolone, Lilly)
Cordran™-N (flurandrenolone with neomycin sulfate, Lilly)

Product brochure available; write Eli Lilly and Company, Indianapolis 6, Indiana.



with NEW

'ACTIFED-C' brand EXPECTORANT

ANTITUSSIVE · EXPECTORANT · BRONCHODILATOR · DECONGESTANT · ANTIHISTAMINIC

The etiology of cough is such that drug therapy designed to produce relief may be called upon to provide several therapeutic actions simultaneously. The ingredients of 'Actifed-C' Expectorant were selected because they produce desirable antitussive, expectorant, bronchodilator, decongestant and antihistaminic effects.

Each 5 cc. teaspoonful contains:

'Actidil'® brand Triprolidine Hydrochloride	2 mg.
'Sudafed'® brand Pseudoephedrine Hydrochloride	30 mg.
Codeine Phosphate	10 mg.
Glyceryl Guaiacolate	100 mg.

Dosage: Adults and children over 12 years—2 tsp., 4 times daily. Children 6 to 12 years—1 tsp., 4 times daily. Infants and children up to 6 years—½ tsp., 4 times daily.

Precaution: Although pseudoephedrine hydrochloride causes virtually no pressor effect in normotensive patients, it should be used with caution in patients with hypertension. In addition, even though triprolidine hydrochloride produces only a low incidence of drowsiness, appropriate precautions should be observed.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York


Schering
checks
"runaway"
allergic
reactions
METRETON®
corticoid-antihistamine compound TABLETS
For complete details, consult latest Schering literature available from your Schering Representative or Medical Services Department, Schering Corporation, Bloomfield, N. J.
S-962

when allergy looms large in the life of your patient...

BENADRYL provides a twofold therapeutic approach to the management of distressing symptoms of food allergy. ■ **Antihistaminic action** relieves urticaria, edema, pruritus, and coryza. ■ **Antispasmodic action** affords relief of gastrointestinal spasm, abdominal pain, nausea, and vomiting.

BENADRYL Hydrochloride (diphenhydramine hydrochloride, Parke-Davis) is available in a variety of forms including: Kapseals,® 50 mg.; Capsules, 25 mg.; Emplets® (enteric-coated tablets), 50 mg.; Aqueous Solutions: 1-cc. Ampoules, 50 mg. per cc.; 10- and 30-cc. Steri-Vials,® 10 mg. per cc.; Elixir, 10 mg. per cc.; Cream, 2% (water-miscible base); and Kapseals [illegible] mg. BENADRYL Hydrochloride with 25 mg. ephedrine sulfate. See [illegible] for details of administration, precautions, and dosage.

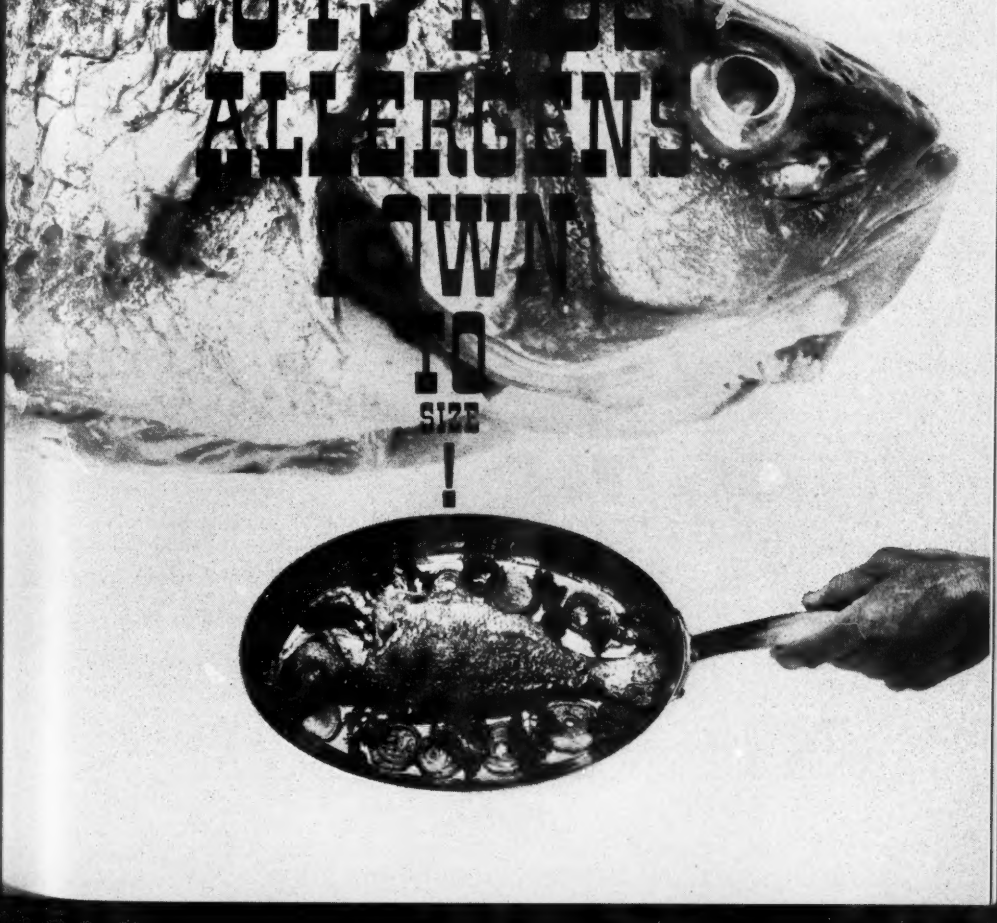
PARKE-DAVIS

PARKE, DAVIS & COMPANY, Detroit 32, Michigan

BENADRYL®

diphenhydramine hydrochloride

CUTS MOST ALLERGENS DOWN TO SIZE!



Since May 11, Synalar Cream has cleared many previously intractable dermatoses. Have you evaluated it in your practice?

On May 11, 1961, Synalar Cream was introduced to the medical profession as "a new[1] topical steroid, a new base, a new standard of effectiveness."

Clinical evidence since its introduction continues to point to its efficacy in speeding remission of many dermatoses previously resistant to other topical steroids. Robinson[2] studied Synalar in 149 patients with dermatoses usually seen in the dermatologist's office; 137 benefited from Synalar therapy, only 12 were unimproved.

What accounts for Synalar performance? First, it has 40 times the topical potency of hydrocortisone. Second, a specially prepared cream base smooths on easily over inflamed lesions in sparing amounts. Proved non-sensitizing in repeated insult patch tests on 200 patients, this water-washable base is odorless, non-staining, and cosmetically acceptable even to the fussiest patient.

If you have not already done so, Syntex invites you to make your own Synalar evaluation.

1. Select three of your most stubborn cases—dermatoses refractory to previous topical steroid therapy or hitherto responsive only to the systemic corticosteroids.
2. Treat them with Synalar Cream for two weeks.
3. Judge the results.

New 5 Gm. Size Now Available

Synalar is now available in an economical 5 Gm. tube, in addition to the original 15 Gm. tube.

For a complimentary starter supply for three patients, please use the coupon below.

References: 1. Mills, J. S., *et al.*: J. Am. Chem. Soc *82*:3399 (July 5) 1960. 2. Robinson, H. M., Jr. A.M.A. Arch. Dermat. *83*:149 (Jan.) 1961.

Dosage and Administration: Synalar (0.025%) Cream is for topical use only. A small amount should be applied lightly to the affected skin area two or three times daily, as needed. The cream should be massaged gently and thoroughly until it disappears. Since Synalar is in a water-washable, vanishing cream base, it is easily applied and leaves no traces. Synalar may be used over long periods of time in specific conditions when deemed necessary.

Precautions: Synalar Cream is virtually non-sensitizing and non-irritating. If idiosyncrasies are encountered, Synalar should be discontinued and appropriate steps taken. In areas of infection, concomitant antibacterial therapy may be indicated. In some instances, when an emollient effect is desired, dilution of the cream with equal parts of hydrogenated vegetable oil or petrolatum makes it more acceptable and effective.

Supplied: 15 Gm. collapsible tubes. Available on prescription only.

synalar® cream **15 Gm.**

0.025% fluocinolone acetonide, Syntex

SYNTEX STEROIDS IN MEDICINE

Medical Department, Syntex Laboratories, Inc.
10 East 40th Street, New York 16, N. Y.
Please send me starter doses of Synalar Cream.

Name (please print) _____

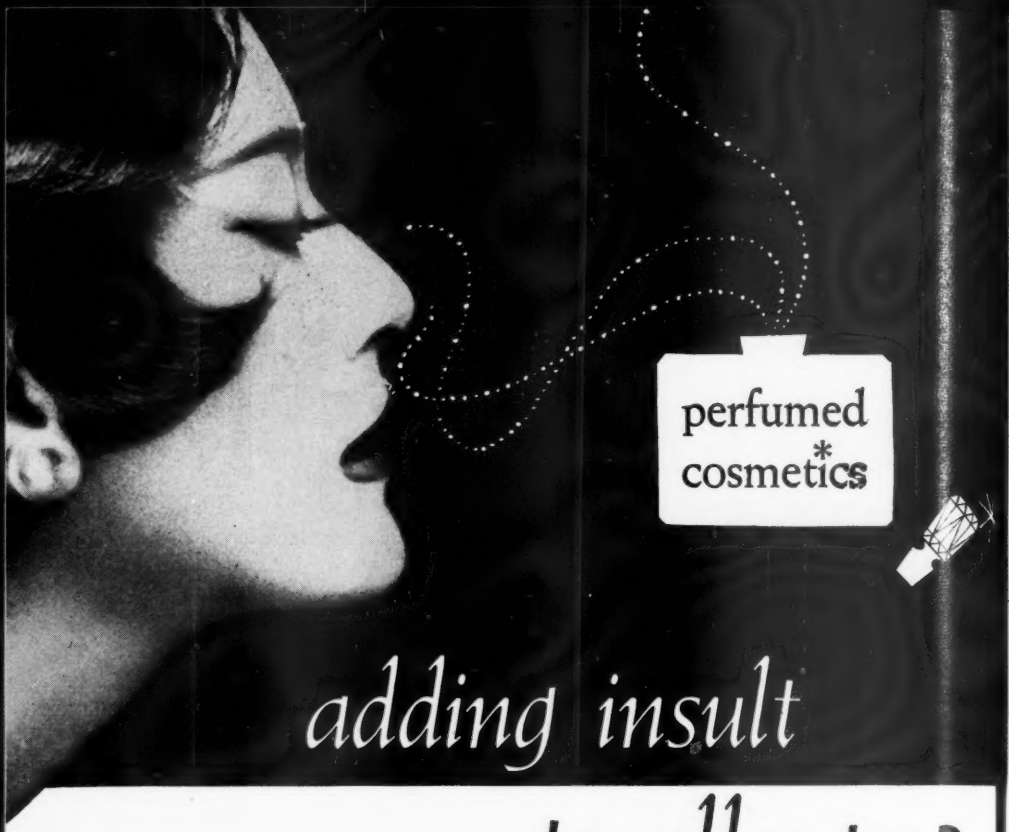
Address _____

City & State _____

Field of practice _____

DEPT. A

Contents for December, 1961



adding insult to allergy?

PERFUMES CAN AGGRAVATE SYMPTOMS

Patients sensitive to one inhalant are usually sensitive to other substances. Perfumes are composed of many chemicals and can superimpose added irritants upon already sensitized membranes. It's safer for these patients to use AR-EX UNSCENTED COSMETICS. These are completely free of natural flower oils, aromatic chemicals and other common cosmetic irritants and allergens—yet are as beautifying as they are safe. Send for free Formulary.

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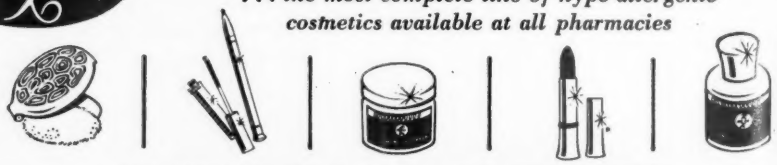


FOR NORMAL SKINS WHEN MILDNESS IS DESIRED
FOR ALLERGIC SKINS WHEN IRRITANTS MUST BE AVOIDED

FOR EFFICIENT TOPICAL MANAGEMENT OF ECZEMATOID DERMATITIS AND OTHER SKIN DISORDERS

new methatar Creme

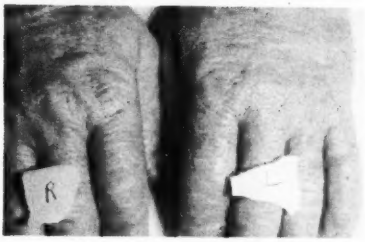
amino acid/antiseptic
with Liquor Carbonis Detergens

"objectively [in a series of 13 patients]* there was little difference between the hydrocortisone cream and Methatar"

Severe infectious eczematoid dermatitis, recurrent over one year

Improvement after 4 days' treatment with (L) hydrocortisone and (R) METHATAR

Severe chronic hand eczema of one year's duration



Improvement after 10 days' treatment with (L) hydrocortisone and (R) METHATAR

*Wise, L. J., Jr., and Derbes, V. J.: Evaluation of Methatar in eczema, South. M. J. 54:1031, Sept., 1961.

EXTENDING THE "metha" BENEFITS TO MORE PATIENTS IN A WIDER AREA OF DERMATOLOGIC USAGE

new methatar* Creme

Composition: An amino acid/antiseptic formulation consisting of a protein hydrolysate, methionine, benzethonium chloride, and Liquor Carbonis Detergens.

relieves itching and burning and promotes healing through the tissue-regenerative action of a protein hydrolysate reinforced by the amino acid, methionine

guards against secondary infection due to pyogenic staphylococci and other organisms by providing the antiseptic, germicidal effect of benzethonium chloride

helps establish a physiologic epidermal pH through the buffering action of the protein hydrolysate

affords the soothing relief of an emollient, water-washable vehicle (DERMABASE*)— nonstaining and greaseless

provides complementary control of itching and curbs inflammation and exudation through the antipruritic, anti-inflammatory, and drying action of the coal-tar derivative, Liquor Carbonis Detergens

extends the benefits of topical amino acid/antiseptic therapy to patients of all ages — in the youngest to the oldest

Note: Available on request — The Borden Company's Concise Guide to Treatment of Skin Disorders with "METHA" Topicals

AND TO PROVIDE FLEXIBILITY OF CHOICE FOR INDIVIDUALIZED TREATMENT

new methaphor* Ointment

Composition: An amino acid/antiseptic formulation consisting of a protein hydrolysate, methionine, camphor, and benzethonium chloride.

for minor skin disorders — affords prompt symptomatic relief, rapid healing, and protection against secondary infection

new methaseptic* Powder

Composition: An amino acid/antiseptic formulation consisting of methionine and benzethonium chloride, together with zinc lactate, as a mild astringent and antiseptic.

for use as a wet dressing or soak in acute dermatitis, and in exudative and chronic eczema

Supplied:
METHATAR Creme — 1½ oz. tubes
METHAPHOR Ointment — 1½ oz. tubes
METHASEPTIC Powder — Package of 12 envelopes

*TRADEMARK OF THE BORDEN COMPANY

Borden's PHARMACEUTICAL DIVISION
350 Madison Avenue
New York 17, N. Y.

a breathing spell from asthma

Quadrinal*

a rapid way to clear the airway

- **stops wheezing**
- **increases cough effectiveness**
- **relieves spasm**

In chronic disorders associated with obstructed respiration, the dependable antispasmodic and expectorant action of Quadrinal rapidly clears the bronchial tree. Patients breathe more easily and acute episodes of bronchospasm are often eliminated. Quadrinal is well tolerated, even on prolonged administration. The potassium iodide in Quadrinal provides an expectorant of time-tested effectiveness and safety.

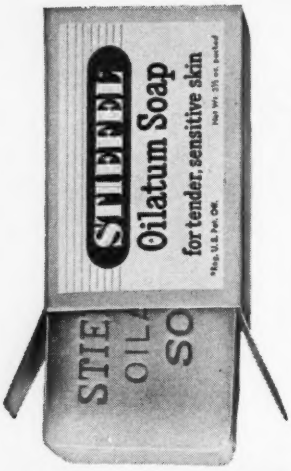
Indications: Bronchial asthma, chronic bronchitis, pulmonary fibrosis, pulmonary emphysema.

Quadrinal Tablets, containing ephedrine HCl (24 mg.), phenobarbital (24 mg.), 'Phyllicin'* (theophylline-calcium salicylate) (130 mg.), **and potassium iodide** (0.3 Gm.)

Also available—
a new Quadrinal dosage form with taste-appeal for all age groups:
fruit-flavored QUADRINAL SUSPENSION (1 teaspoonful = 1/2 Quadrinal Tablet)

KNOLL PHARMACEUTICAL COMPANY, ORANGE, NEW JERSEY

*Quadrinal, Phyllicin®



Super-Oiled

Oilatum® Soap

hypoallergenic cleanser

for tender, sensitive skin.

- Super-oiled (not super-fatted) to minimize "drying"
- 600% higher content of unsaturated oils than other cleansers
- Rich, oil-laden lather, even in hard water
- Ideal for pediatric and geriatric use
- Available scented or unscented

COMPLEMENT
DON'T COMPLICATE
SKIN TREATMENT

Super-moisturized

Oilatum® Cream

(new improved formula)

for dry, thirsty skin.

- An oil-in-water emulsion buffered to pH 5.5
- Leaves "the film that breathes" . . . retards moisture loss
- Contains highly unsaturated vegetable oils . . . no lanolin or mineral oil
- Cosmetically pleasant . . . scented or unscented

You can recommend STIEFEL Oilatum Cream with confidence for symptomatic therapy of dry, tender or sensitive skin, lanolin or alkali-sensitivity, ichthyosis, winter itch, wind burn and similar etiologic entities.

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Logical Dermatologicals—Since 1847

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in asthma bronchitis cystic fibrosis

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ORGANIDIN, the mucolytic expectorant, combines the properties of iodides and glyceryl ethers; is equally effective[2,3] as saturated solution of potassium iodide, yet contains 1/30 the amount of iodine; is better tolerated[2,3,5,6,7]; has a more sustained action[4], and is virtually free of side-effects . . . even in 7 out of 10 patients who are sensitive to iodides[5].

ORGANIDIN is available in: Elixir, 1.2%, bottles of 16 oz.; Solution, 5%, bottles of 30 cc.; Tablets, 30 mg., bottles of 100.

References: 1. Shwachman, H.: Personal communication (cystic fibrosis). 2. Seltzer, A.: To be published in Med. Ann. Dist. of Col. 3. Bickerman, H. A.: Personal communication. 4. Hoffnagle, G. F. and Osol, A.: J.A.Ph.A., *17*, 149-153. 5. Fontana, V. J.: Inter. Corresp. Soc. of Allergists, XXIII, 185. 6. Segal, M.S.: Ibid, 205. 7. Friend, D. G.: N. E. Jl. Med., *263*:1358-1360, Dec., 1960. 139WS

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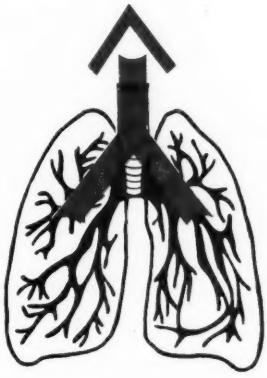

assure diagnostic and therapeutic success [1] [2] [3]

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(1) Silbert, N. E., Ciba Clinical Symposia, 6: 86 May 1954

(2) Mechaneck, I., Annals of Allergy, 12: 164 March 1954

(3) Rosen, F. L., J. Med. Soc. N.J., 51: 110 March 1954